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# CHLOROTHIAZIDE AND HYDROCHLOROTHIAZIDE IN MANAGEMENT OF HYPERTENSION

BY

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The advent of chlorothiazide constituted an important advance in the management of hypertension. It has proved of value as an adjuvant to other hypotensive drugs (Tapia *et al.*, 1957; Heider *et al.*, 1958; Barnett and Marshall, 1958; Freis *et al.*, 1958; Rochelle *et al.*, 1958). In some cases it is effective when used alone (Hollander and Wilkins, 1957; Hall and Owen, 1959).

As a diuretic agent hydrochlorothiazide has been found to be equally active in a dosage between one-tenth and one-twentieth that of chlorothiazide (Richterich, 1958; Ford, 1959; Moyer *et al.*, 1959; Fleming *et al.*, 1959).

In the present communication our clinical findings in the use of these drugs, alone and in combination with other hypotensive agents, are reviewed. A detailed comparative study of the effects of electrolyte and fluid excretion produced by the two drugs, together with observations on their mode of action in lowering blood-pressure, will be presented elsewhere (McQueen and Morrison). However, certain observations on the practical differences between the two drugs are contained in this paper.

## Method

Blood-pressures while under treatment were assessed on day tests at the hypertensive clinic, during which six to eight readings in the sitting and standing posture were recorded. The figures quoted are the means of the average blood-pressures in each posture. The basal blood-pressure was recorded by the technique as recommended by Smirk (1957), after a night in hospital following heavy sedation with pentobarbitone. Chlorothiazide (C.) or hydrochlorothiazide (H.C.) was either added to an existing regime consisting of a ganglion-blocking agent or a rauwolfia alkaloid, or a combination of such drugs, or given at the beginning of treatment, with subsequent addition of other drugs. Cases in which C. or H.C. was added to a regime already in operation had in general either somewhat unsatisfactory blood-pressure control—as reflected in the tables illustrating the effects of addition of C. or H.C.—or had satisfactory control only at the cost of undue side-effects. It is advisable on addition of C. or H.C. to reduce the dosage of ganglion-blocking agent often to approximately two-thirds of the original.

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## Findings

In a total clinic population of some 400 patients who attended regularly, C. or H.C. has been used in 203 cases either as an adjuvant to the existing regime or, exceptionally, as the sole form of therapy.

In most instances the dosages used were C., 500 mg., and H.C., 50 mg., twice daily. All patients were given potassium chloride as 0.33-g. sugar-coated tablets in a daily dosage of 1 to 2 g. In addition, they were advised to include plenty of fruit or fruit juice in their diet whenever possible. The definitive form of therapy adopted in 203 cases is shown in Table I.

TABLE I.—*Definitive Form of Therapy in* 203 *Patients Receiving Trial of Chlorothiazide or Hydrochlorothiazide*

| | |
|---|---|
| C. or H.C. plus ganglion-blocking agent ± rauwolfia alkaloid | 147 |
| ,, ,, ,, ,, rauwolfia alkaloid .. .. .. .. | 26 |
| ,, ,, ,, alone .. .. .. .. .. .. .. | 30 |

### Use in Association with Ganglion-blocking Agents

The amount of ganglion-blocking agent required for a satisfactory regime was considerably reduced. Many patients in whom parasympathetic side-effects made the regime excessively uncomfortable were very much improved. When frequent episodes of postural hypotension occurred with a dosage of ganglion-blocking agent adequate to maintain satisfactory levels, addition of C. or H.C. and appropriate reduction of the dosage of the ganglion-blocking drug often enabled fully satisfactory control to be maintained without the occurrence of such episodes. Nine patients out of 119 were eventually able to dispense with ganglion-blocking drugs. The results of those cases in which we have multiple readings at day tests before and after the addition of C. or H.C. to the regime are shown below. Dosage reduction was evident with both quaternary ammonium compounds and the secondary and tertiary amine ganglion-blocking agents (Table II). It should be pointed out that these patients were selected because blood-pressure control in many was unsatisfactory. Blood-pressure levels after addition of C or H.C. were lower than before (Tables III and IV), and

TABLE II.—*Dosage Requirement of Ganglion-blocking Agent for Satisfactory Hypotensive Regime Before and After Addition of C. or H.C. (mg. per 24 Hours)*

| | Pentolinium (31 Patients) | Mecamylamine (17 Patients) | Pempidine (14 Patients) | Chlorisondamine (6 Patients) |
|---|---|---|---|---|
| Before .. | 535 | 41·6 | 22·4 | 554 |
| After .. | 403·5 | 28·5 | 16·1 | 329 |
| Reduction | 24% | 31% | 28% | 41% |

TABLE III.—*Pentolinium* (31 *Cases*) *Blood-pressure in mm. Hg*

| | | Mean of Averages of Day Tests | | Mean of Trough Pressure |
|---|---|---|---|---|
| | | Sitting | Standing | Standing |
| Before addition of C. or H.C. | Systolic | 180·3 S.D. 24·0 | 177·3 S.D. 24·8 | 156·9 S.D. 27·2 |
| | Diastolic | 108·2 S.D. 15·3 | 107·9 S.D. 17·1 | 97·4 S.D. 20·4 |
| After addition of C. or H.C. | Systolic | 151·9 S.D. 13·0 | 148·6 S.D. 15·8 | 129·2 S.D. 19·7 |
| | Diastolic | 97·1 S.D. 9·1 | 97·3 S.D. 10·1 | 86·4 S.D. 12·5 |

TABLE IV.—*Mecamylamine* (17 *Cases*). *Blood-pressure in mm. Hg*

| | | Mean of Averages of Day Tests | | Mean of Trough Pressure |
|---|---|---|---|---|
| | | Sitting | Standing | Standing |
| Before addition of C. or H.C. | Systolic | 175·3 S.D. 16·5 | 177·7 S.D. 20·9 | 159·6 S.D. 20·4 |
| | Diastolic | 105·7 S.D. 7·7 | 108·7 S.D. 9·8 | 100·0 S.D. 10·4 |
| After addition of C. or H.C. | Systolic | 147·1 S.D. 19·3 | 142·9 S.D. 20·2 | 127·7 S.D. 21·0 |
| | Diastolic | 92·5 S.D. 14·0 | 92·2 S.D. 14·9 | 84·8 S.D. 17·7 |

therefore the degree of dosage reduction was probably somewhat less than in cases in which blood-pressure levels before and after addition of C. or H.C. were the same.

In Tables III and IV the means of the averages of day tests before and after the addition of C. or H.C. to regimes including pentolinium and mecamylamine illustrate the improved control. Similar changes were observed with pempidine and chlorisondamine.

### C. or H.C. Plus a Rauwolfia Alkaloid

In 26 cases C. or H.C. plus a rauwolfia alkaloid proved the most satisfactory regime. Reserpine was most commonly employed, but rescinnamine and canescine were used in some, especially when there appeared to be any special risk from depression. Considerable increase of the hypotensive action was obtained when rauwolfia alkaloids were combined with H.C. or C. Table V shows the effect of the addition of one of the diuretic agents in 13 patients who were receiving a rauwolfia alkaloid alone (as assessed by the average of day tests before and after).

TABLE V.—*Addition of C. or H.C. Agent in* 13 *Cases Where Rauwolfia Alkaloid Was Being Used Alone*

| | Mean of Averages of Day Tests | | Significance of Difference |
|---|---|---|---|
| | Before Addition | After Addition | |
| Systolic .. | 171·8 S.D. 20·6 | 146·1 S.D. 19·0 | $P<0.001$ |
| Diastolic .. | 106·6 S.D. 13·2 | 93·6 S.D. 8·4 | $P<0.001$ |

### C. or H.C. Alone

A total of 30 cases have been maintained on C. or H.C. as the sole hypotensive agent. The averages of day test readings on these drugs have been compared with the basal blood-pressure. In Table VI it will be seen that, in 21 of such patients in whom both sets of data are available, the average systolic pressure on treatment fell below the systolic basal level. The diastolic value was the same.

The cases in which satisfactory control was obtained with diuretic agents alone or in conjunction with rauwolfia alkaloids were, in general, of less severity than those in which a ganglion-blocking agent was required.

Two indices are used to demonstrate this difference, the basal blood-pressures and the appearances in the fundus oculi. They are illustrated in Tables VII and VIII.

Table VII is a comparison of the basal blood-pressures. Those who required ganglion-blocking drugs will be seen to have a significantly higher basal blood-pressure. The fundal grading (Keith *et al.*, 1939) also demonstrates the greater severity of those on ganglion-blocking drugs (Table VIII). However, one patient who was treated initially with ganglion-blocking drugs for malignant hypertension is now well maintained on C. alone.

A number of cases with evidence of cerebral or myocardial ischaemia presented for treatment. These require special caution in management with the more powerful hypotensive agents, and control was preferred for many of them by C. or H.C. alone or in combination with a rauwolfia alkaloid. Of the 56 patients on one or other of the above regimes, 27 presented with evidence of cerebral or myocardial ischaemia. The smoother control obtained with the addition of a diuretic to the ganglion-blocking drug greatly benefited those who still required the more powerful agents.

TABLE VI.—*Basal Blood-pressure and Averages of Day Tests in* 21 *Cases Receiving C. or H.C. Alone*

| | | | |
|---|---|---|---|
| Systolic | Basal B.P. .. | 154·8 S.D. 13·8 | $0.05>P>0.02$ |
| | C. or H.C. .. | 146·5 S.D. 15.1 | |
| Diastolic | Basal B.P. .. | 95·5 S.D. 12·8 | Not significant |
| | C. or H.C. .. | 96·0 S.D. 8·8 | |

TABLE VII.—*Basal Blood-pressures of Patients on Three Regimes*

| | C. or H.C. + G.B. Agent | C. or H.C. + Rauwolfia | C. or H.C. Alone |
|---|---|---|---|
| Systolic .. | 174·7 S.D. 22·2 | 150·7 S.D. 20·8 | 154·8 S.D. 13·8 |
| Diastolic .. | 107·4 S.D. 15·9 | 94·6 S.D. 18·0 | 95·5 S.D. 12·8 |

TABLE VIII.—*Fundal Grading of Patients on Various Regimes*

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| C. or H.C. alone .. | 14 | 9 | 6 | 1 |
| C. or H.C. + rauwolfia .. .. | 7 | 14 | 5 | 0 |
| C. or H.C. + G.B. agent ± rauwolfia | 18 | 68 | 49 | 12 |

### Toxic and Unwanted Side-effects

Of 170 patients who received C., 33 (19.4%) had specific complaints following the inception of therapy, while similar troubles were reported by 8 (13.1%) of the 61 patients receiving H.C. They were for the most part transitory, and are detailed in Table IX.

With the exception of one case with an acute sensitivity rash, all toxic effects of H.C. were much less severe. Nine persons stopped C., six with severe nausea and epigastric discomfort, one with severe palpitations, one with a sensitivity rash, and one with severe dysuria. Of those with gastric irritation, five were changed to H.C. with immediate benefit, only one retaining slight epigastric discomfort for a few days. The patient with severe dysuria had no further discomfort after being transferred to H.C.

TABLE IX.—*Toxic and Unwanted Side-effects*

| | C. | C.H. |
|---|---|---|
| Nausea and epigastric discomfort | 19 | 2 |
| Dysuria | 5 | 2 |
| Skin irritation | 3 | 1 |
| ,, sensitivity | 1 | 1 |
| Weakness and lethargy | 2 | 2 |
| Digitalis toxicity | 1 | |
| Palpitations | 1 | |
| Metabolic acidosis | 1 | |
| | 33 (19·4%) | 8 (13·1%) |

Of 19 cases on maintenance digitalis, one female developed hypokalaemia and digitalis toxicity shortly after C. was started. This was controlled only after increasing the dose of potassium chloride to 8 g. daily. A further disadvantage of C., with its particular tendency to induce loss of bicarbonate, was seen in a 42-year-old man in whom renal impairment had resulted in a mild metabolic acidosis. When C. was added, his general condition rapidly deteriorated owing to a severe reduction of his bicarbonate reserve. This was relieved on cessation of C. He was subsequently maintained satisfactorily on a small dose of H.C. Initial weakness and lethargy have been noted on both drugs, a fact well known to occur with mersalyl; this may be due to a combination of acute reduction of plasma volume and electrolyte depletion.

We have no explanation for the puzzling dysuria present during the first week of treatment and common to both drugs.

Two men had well-documented severe hypotension, which occurred on the second day of treatment with H.C. 100 mg. daily by itself. They have since been satisfactorily controlled with H.C. 50 mg. daily.

## Discussion

On the basis of the experience now available it is possible to evaluate the place of C. and the newer derivative H.C. in the management of hypertension.

The assessment of hypotensive agents requires an adequate basis for comparisons. Casual blood-pressure readings are notoriously unsatisfactory for this purpose. The state of the fundi has become the traditional method of comparison of groups of hypertensive subjects, but it is highly desirable to have also some standard and reproducible estimate of the pretreatment blood-pressure both as a basis for comparison of cases and as a standard against which to compare the results of treatment. In the present communication use has been made of the basal blood-pressure as a means of adjudging the degree of severity of the cases under observation. Reduction of blood-pressure to or below the basal blood-pressure in the unsedated ambulant patient implies active blood-pressure reduction beyond the range which would be expected from the effects of a placebo.

The assessment of the effect of therapy also has been carried out under standard conditions at the hypertensive clinic, employing a series of six or eight observations documenting the range of diurnal variation as well as the mean. In addition, the effect of posture is expressed by readings in both sitting and standing postures. An important factor limiting dosage in the control of blood-pressure with ganglion-blocking agents is the "trough" blood-pressure, or lowest level to which the blood-pressure falls in the standing posture.

With these methods it can be seen that C. or H.C. alone can produce a fall in blood-pressure to, or even below, the basal blood-pressure, and that in a number of patients (15% approximately of those attending our clinic who have been given a trial with these drugs), this constituted the optimum form of therapy. These patients were characterized by a somewhat lower average basal blood-pressure than those who required in addition, the use of a ganglion-blocking agent. However, they included a considerable number of patients with complicating cerebral or myocardial ischaemia in whom use of the ganglion-blocking agents constituted a greater hazard. A further 13% approximately of the total were adequately controlled on C. or H.C. plus a rauwolfia drug. Again these patients had an average basal blood-pressure which was significantly lower than that of the group requiring a ganglion-blocking agent. This group also included a number of patients with ischaemic complications.

The majority of our patients still required the use of a ganglion-blocking agent, and in these the adjuvant effect of C. or H.C. has been marked, producing improved control associated with reduction in the dose of the ganglion-blocking agent. As a result there has been a valuable decrease in the incidence and severity of parasympathetic side-effects. During restabilization, postural hypotension has occasionally become more apparent, but eventually it is usually less troublesome. This has been particularly advantageous in those patients in whom cerebral or myocardial insufficiency had previously appeared at the depth of the trough. After the readjustment many commented on their increased alertness and well-being—presumably a further benefit of reduced ganglion-blocking dosage.

Harington and Kincaid-Smith (1958) demonstrated that the non-quaternary ganglion-blocking agent mecamylamine was excreted more rapidly in an acid than in an alkaline urine. Pempidine, which is excreted by the same mechanism (Harington and Kincaid-Smith, 1958), is probably similarly affected. The alkalinization of the urine resulting from the carbonic anhydrase inhibitor effect of (particularly) chlorothiazide might therefore have been expected to produce a more marked enhancement of hypotension in cases where these compounds were being used than with quaternary ammonium compounds. However, the degree of dosage reduction compatible with maintenance of equivalent, or better, blood-pressure control, though greater with mecamylamine and pempidine than with pentolinium, was actually less than that found in the case of chlorisondamine, though the number of cases on the latter was small. Other agents were used in numbers too small for results to be significant.

There is no evidence that mild or moderate renal impairment reduces the efficiency of C. or H.C., but caution is necessary if there is an abnormal serum acid-base or electrolyte pattern. Reference to this is made later. Apart from minor alterations of the sodium/potassium ratio in the urine, the only important difference between the two drugs appears to be in the incidence and severity of the toxic and unwanted side-effects. In this respect H.C. appears to be an improvement on C., though both drugs produce similar untoward reactions. Fortunately, most symptoms were transitory: nausea and epigastric discomfort were most commonly encountered, probably the result of local irritation.

Dysuria was met with in both sexes, in some accompanied by a mild ache in the loins. The former symptom was severe enough in one patient on C. to

make him unwilling to continue treatment. Acute retention in association with prostatic hypertrophy occurs with mercurial diuretics, but to date we have not encountered this problem. As it would occur during the initial diuresis, it is safer to give elderly men half the recommended dosage for the first week.

Both drugs have produced typical acute skin sensitivities, and in addition an itch, which tends to remain much longer than other side-effects. Being sulphonamides, caution is necessary in prescribing C. or H.C. for patients with a history of sulphonamide sensitivity.

Of patients who were forced to stop C., six were transferred to H.C., only one reporting continuance of mild symptoms.

On a normal diet excessive depletion of body sodium has not occurred. However, in patients with congestive heart failure a restricted intake of sodium may produce the salt-depletion syndrome. More important is the increased potassium excretion which is common to both drugs. To compensate, we have given supplementary potassium chloride 1–2 g. daily. Potassium lack, in the presence of ischaemic heart disease, may precipitate cardiac arrhythmias. The association of potassium depletion and digitalis toxicity is well established (Lown *et al.*, 1951), and this phenomenon has been reported with C. (Pfeiffer, 1958; Freis, 1959). Particularly close attention to serum potassium levels is necessary in cases of ischaemic heart disease with failure, and one such case of ours required 8 g. of potassium chloride daily before the serum potassium returned to the pre-treatment level. Chronic potassium depletion may also produce renal lesions, mainly tubular and initially reversible (Relman and Schwartz, 1956), but which may later become permanent. Metabolic acidosis is often a concomitant of renal impairment, and the further depletion of bicarbonate reserve induced by C. may be especially disadvantageous under these circumstances (Watson *et al.*, 1958). H.C. may in this context be the safer of the two.

Bone-marrow depression, though recorded, is very rare, and we have not experienced it. Laragh *et al.* (1958) found that C. raised the serum uric acid, and others have reported the occurrence of joint pain, but we did not observe any such episodes in three patients with chronic gout.

### Summary

Chlorothiazide and hydrochlorothiazide are important additions to the list of hypotensive drugs, and in this respect seem equally effective in doses of 500 mg. for C. and 50 mg. for H.C. Both drugs enhance the effect of ganglion-blocking agents and diminish their requirement for satisfactory blood-pressure control with consequent diminution in parasympathetic side-effects. The enhancement is obvious with quaternary ammonium compounds as well as with compounds such as mecamylamine and pempidine.

Of 203 patients receiving these drugs, 15% were managed most satisfactorily with C. or H.C. alone; 13% were controlled by a combination with a rauwolfia alkaloid. Though these patients, assessed in terms of the basal blood-pressure as well as fundal grading, were somewhat less severely hypertensive than those requiring ganglion-blocking agents, they nevertheless included a considerable proportion with completing cerebral or myocardial ischaemia, making their management in other ways difficult.

H.C. certainly had less tendency to induce gastro-intestinal and possibly other side-effects. This gives it certain practical advantages over C. Care must be taken to avoid potassium depletion with both drugs.

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## COMPARISON OF TRIMETHIDINIUM AND PEMPIDINE IN TREATMENT OF SEVERE HYPERTENSION

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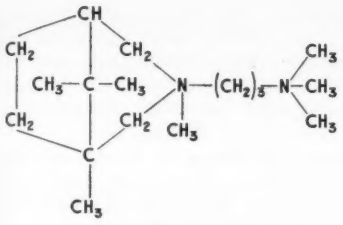
The value of ganglion-blocking agents in the treatment of severe hypertension is well established (Smirk, 1954; Sears *et al.*, 1959), but because of the frequency and severity of the side-effects they produce there is a constant search for effective drugs which can be used reliably by mouth and have a minimum of unwanted side-effects. In this paper we describe our experience with two recently developed ganglion-blocking agents, trimethidinium and pempidine, and have tried to assess some of their advantages and drawbacks.

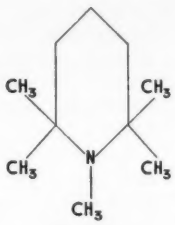
### Chemistry and Pharmacology

Trimethidinium (see formula) is an ionized quaternary ammonium compound (as is pentolinium), differing from pentolinium in that the two groupings on each nitrogen atom are different. Absorption from the gastro-intestinal tract is incomplete but usually fairly constant in any one person; excretion is in the urine.

Pempidine has the formula shown, and is an unionized tertiary amine (mecamylamine is a secondary amine).



TRIMETHIDINIUM



PEMPIDINE

It is freely absorbed from the gastro-intestinal tract and distributed throughout the body fluids. Excretion in the urine is decreased by rendering the urine alkaline.

Both drugs act primarily by inhibition of transmission of nerve impulses through both sympathetic and parasympathetic ganglia of the autonomic nervous system, and may also have central actions on the brain. Pempidine, but not trimethidinium, has been shown to depress the peristaltic activity of guinea-pig ileum, and, in very large doses, to cause neuromuscular blockade, tremors, and ataxia.

Because of the rapid urinary excretion of pempidine, its length of action is much shorter than that of trimethidinium, and the dosage, therefore, has to be at shorter intervals. As with other ganglion-blocking agents, they have to be used with caution in cases with severe renal impairment.

## Selection of Patients

The criteria used for selecting the 24 patients in this series were those previously described (Sears *et al.*, 1959), and the technique by which they were stabilized on one or other drug was identical. The patients were divided into two equal groups, 12 receiving trimethidinium and 12 pempidine. Allocation to one group or the other was random at first, but it soon became obvious that the groups were not comparable after the first eight cases, and thereafter patients were allocated in such a way as to try to keep the two groups broadly similar in age, sex, and severity of hypertension. Details of the two groups are shown in Table I.

TABLE I

| | Trimethidinium | Pempidine |
|---|---|---|
| No. of patients | 12 | 12 |
| Age range (years) | 25–63 | 27–55 |
| Mean age | 48 | 46 |
| Sex ratio M : F | 9 : 3 | 9 : 3 |
| Blood urea greater than 40 mg./100 ml. | 7 | 5 |
| Retinopathy Grade IV | 6 | 6 |
| Retinopathy ,, II or III | 4 | 4 |
| Retinopathy ,, I | 2 | 2 |
| Deaths | 2 | 4 |
| Mean diastolic B.P. (mm. Hg) | 140 | 142 |

## Results

*Frequency of Dosage.*—Certain important differences were immediately noted between the two drugs under trial. Pempidine acted slightly sooner and its effect had worn off much faster than that of trimethidinium, and in consequence pempidine was usually given in four daily doses, whereas trimethidinium usually gave adequate control with two doses each day. The dose range; the frequency with which the doses had to be given; the times at which the fall in blood-pressure usually started, reached a maximum, and had largely worn off, are given for each preparation in Tables II and III. The action of both drugs was prolonged in patients with impaired renal function, and accumulation could occur in these patients, especially with trimethidinium.

*Tolerance.*—This was noted in 5 out of 12 patients on trimethidinium and in 4 out of 12 on pempidine, and it seemed of greater degree with trimethidinium.

*Effect of Reserpine.*—In five patients in each group it was possible to determine whether or not reserpine had potentiated the action of either drug. Four of the five patients on trimethidinium showed potentiation, some to a very marked degree, while only two of the pempidine group showed some potentiation, and this was to a less extent than with those on trimethidinium.

TABLE II.—*Frequency of Dosage/24 Hours*

| | No. of Daily Doses | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Trimethidinium (no. of cases) | 1 | 8 | 3 | | |
| Pempidine ,, | | 3 | 2 | 6 | 1 |

TABLE III.—*Duration of Effect and Dose Range*

| | Duration of Effect (Hours) | | | Dose Range (mg.) |
|---|---|---|---|---|
| | Onset | Maximum | Duration | |
| Trimethidinium | 1 | 3–5 | 8–10 | 60–240 |
| Pempidine | ½–1 | 1–3 | 4–6 | 5– 60 |

TABLE IV.—*Type of Side-effect*

| | On Trimethidinium | On Pempidine |
|---|---|---|
| Constipation | 7 cases | 9 cases |
| Visual difficulty | 6 ,, | 5 ,, |
| Dry mouth | 5 ,, | 5 ,, |
| Urinary difficulty | — | 3 ,, |
| Impotence | — | 2 ,, |
| Irregular postural hypotension | 1 case | — |

TABLE V.—*Severity of Side-effects*

| Side-effects | On Trimethidinium | On Pempidine |
|---|---|---|
| None or very mild | 5 cases | 4 cases |
| Moderate, relieved by appropriate measures | 5 ,, | 5 ,, |
| Severe, incompletely relieved | 1 case | 2 ,, |
| Intolerable | 1 ,, | 1 case |

*Side-effects.*—These were assessed after the patients had been on the ganglion-blocking agents for at least three weeks. While it is realized that they may not reflect the final assessment of side-effects, they do, however, show the type of side-effects experienced by the group as a whole. Tables IV and V show the type and severity of the side-effects most commonly met with.

*Effect on Blood-pressure.*—All patients responded to whichever drug they received, and in only two instances were the side-effects such that the blood-pressure could not be significantly reduced at all. The Chart shows the fall in standing diastolic blood-pressure in each of the 24 patients following treatment with either trimethidinium or pempidine. The figures represent the difference between the mean pretreatment in-patient diastolic blood-pressure and the diastolic pressure recorded in the erect posture one or two days before discharge from hospital.

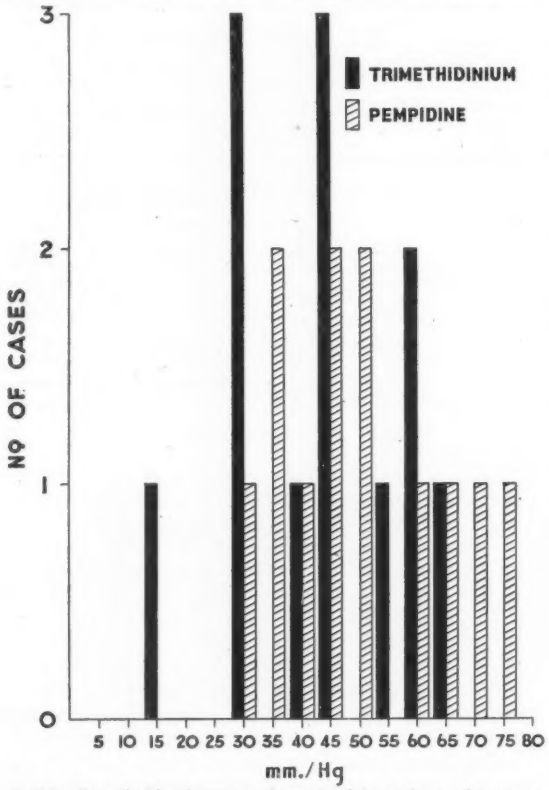
## Out-patient Control

The majority of patients required adjustment of their dosage when first seen as out-patients, the blood-pressure readings being not nearly so satisfactory as those obtained in hospital just before discharge. Control was thereafter generally less satisfactory than when in

hospital, and the particular drawbacks with out-patient management are detailed below.

*Trimethidinium.*—While the prolonged action of this drug was a great help, its main drawback, especially when high doses were employed, was its irregular absorption. This was not a major source of difficulty, but it occurred often enough to be a potential hazard for several patients.

*Pempidine.*—With the procedure in the out-patient clinic that has been previously described (Sears *et al.*, 1959), the short duration of action of pempidine had a distinct disadvantage. We have found that as little as three hours after the first morning dose some patients have had uncontrolled hypertension, though they had complained of undoubted hypotensive symptoms an hour or so previously. For this reason it has been very difficult to be certain whether or not a patient is on the optimum dose of pempidine, except where the action has been prolonged because of poor renal function. By contrast with trimethidinium, pempidine has the advantage of reliable absorption and, in a given patient, a predictable effect.




Fall in diastolic blood-pressure in each of 24 patients after treatment with either trimethidinium or pempidine while in-patients.

In all cases where treatment was given for three months or longer there was a notable improvement in retinopathy, and headaches and exertional dyspnoea were much lessened. The length of follow-up varies from a few weeks to 12 months in the case of both drugs.

## Discussion

The fact that no one ganglion-blocking agent has been generally accepted as the agent of choice in the treatment of severe hypertension is sufficient evidence of their overall similarity. The purpose of this investigation has been to see whether either of these new ganglion-blocking agents offers any advantages over the older ones, particularly pentolinium, which we have found the most satisfactory heretofore (Sears *et al.*, 1959).

Both trimethidinium and pempidine proved effective in lowering the blood-pressure when given orally, and there was an equal incidence of side-effects. However, our impression is that as a rule the constipation caused by trimethidinium is rather less severe than that produced by pempidine. There was one exception to this observation—a patient on trimethidinium whose constipation on one occasion amounted almost to a paralytic ileus.

This relative decrease in severity of constipation has also been noted during treatment with pentacynium (McKendrick and Jones, 1958), which is another of the group of asymmetrical quaternary ammonium compounds to which trimethidinium belongs. Compared with our experience with mecamylamine (Sears *et al.*, 1959), neither trimethidinium nor pempidine produces such severe side-effects; Harington *et al.* (1958) also incline to the view that pempidine will prove less toxic than mecamylamine.

The dosage of both drugs seems more critical than with mecamylamine or pentolinium, and small alterations may produce considerable lowering of the blood-pressure. This is less troublesome with pempidine because its transient action soon allows the blood-pressure to recover. It is, however, a distinct advantage that a patient need take trimethidinium only twice daily, against four or five doses of pempidine. The greatest practical drawback with the out-patient control of subjects taking pempidine is the rapidity with which its effects wear off. Pempidine, however, seems more certain and constant in its action than trimethidinium, which sometimes gives irregular severe postural hypotension.

## Summary and Conclusions

Our experience over the past 12 months in the treatment of 24 patients with severe hypertension, using two new ganglion-blocking agents, is described. The control, side-effects, and out-patient management of the patients are discussed. The major advantage of trimethidinium is less frequent dosage, but this may be offset by the risks of unexpected hypotension. The action of pempidine is more constant and reliable, but its effects wear off quickly, necessitating more frequent medication.

In that its action is more prolonged than pentolinium, trimethidinium is in some respects an improvement on it. This alone does not, at the moment, seem adequate reason for altering the treatment of patients already satisfactorily stabilized on pentolinium, whose control as out-patients, particularly when reserpine is effective, seems the more satisfactory.

We thank Professor D. A. K. Black for his advice on the preparation of this paper, and for allowing us to study patients under his care. We also thank Messrs John Wyeth and Brother, Ltd., for generous supplies of trimethidinium.

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# PLASMA PEMPIDINE CONCENTRATIONS IN HYPERTENSIVES

BY

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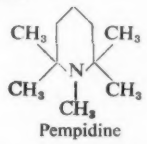
Pempidine (1:2:2:6:6-pentamethylpiperidine) is a fully saturated heterocyclic tertiary amine with a powerful blocking action on autonomic ganglia. It has the following formula:



Pempidine

It is widely used in treating severe hypertension, and when administered orally as the hydrogen tartrate it is completely absorbed and thereafter excreted rapidly in the urine (Harington *et al.*, 1958). Hitherto, concentrations of pempidine in the blood of patients treated with the drug could not be measured because existing analytical methods were too insensitive. However, a technique described by Muggleton and Reading (1959) has now made it possible to estimate the amount of pempidine in plasma from patients having single or repeated (maintenance) oral doses, which embrace the whole range normally used in clinical practice. Plasma pempidine concentrations have therefore been studied with reference to the hypotensive effect of the drug. Also, data obtained from hypertensive out-patients on maintenance treatment have been compared with plasma concentrations of pempidine found in similar patients treated in hospital.

## Materials and Methods

All the patients in this series of studies had severe hypertension with retinitis, hypertensive heart failure, or severe symptoms. Except where otherwise stated, the blood urea was normal.

Preliminary measurements established that the concentration of pempidine in plasma reached its peak some two hours after an oral dose and was negligible at the end of six hours. Throughout the study, except where otherwise stated, blood samples and blood-pressures (lying and standing) were taken just before the dose, and at one, two, four, and six hours thereafter. All blood samples were heparinized, and centrifuged to separate the plasma. The hypotensive response was assessed by the fall in blood-pressure on standing.

Ten fasting patients received their first dose of 2.5 to 10 mg. of pempidine, administered as the hydrogen tartrate either in the standard tablet (eight patients) or dissolved in water (two patients). In three cases urine pased during the six-hour period of observation was collected and the amount of pempidine determined.

Eight patients receiving maintenance treatment in hospital were given 2.5 to 25 mg. of pempidine four times daily, at 6 a.m., noon, 6 p.m., and 11 p.m. The pempidine concentration in plasma and the hypotensive response were measured after the noon dose according to the schedule described above. Two uraemic patients, whose blood-pressures were controlled with twice-daily doses of pempidine, were studied for several days after beginning treatment to find out whether impaired renal function gave rise to progressively increasing concentrations of pempidine in the plasma.

Observations were also made in 30 out-patients during routine visits to the hospital hypertension clinic. Their blood-pressures had all been stabilized with pempidine during a previous stay in hospital. The blood-pressure, lying and standing, was measured, a blood sample was taken, and the time of the last dose (reported by the patient) was recorded. Most of the patients were examined only once, but in four cases estimations were made on two or more occasions.

The methods of analysis of plasma and urine used in the present investigation were largely as described by Muggleton and Reading (1959). Plasma concentrations of pempidine were measured by the eosin fluorescence technique, which was slightly modified to achieve even greater sensitivity than before. A more powerful radiation source was employed (Mazda 250-watt mercury vapour lamp, type ME/D), so that only 1 ml. of plasma was required for the assay. To the plasma was added 0.5 ml. of 10 N sodium hydroxide solution, and the pempidine was extracted with ether ($4 \times 2$ ml.). The base was taken into N hydrochloric acid ($1 \times 0.5$ ml.) to which was next added 0.5 ml. of 10 N sodium hydroxide before extracting the pempidine with xylene ($3 \times 2$ ml.). 5 ml. of this solution and 1 ml. of the eosin reagent were finally mixed in the sample cell and transferred to the fluorescence apparatus. Recoveries were close to 80% and were very reproducible. The blank obtained with plasma which contained no pempidine was rather high ($\equiv 0.045$ $\mu$g. of pempidine per ml.) but showed only very small variations from sample to sample. Thus for 26 samples the pempidine equivalent of the blank was $0.045 \pm 0.002$ $\mu$g./ml., and this value was used throughout the present work. The total error in the plasma concentrations of pempidine is thought not to exceed 0.003 $\mu$g./ml. Estimations of pempidine in urine were carried out by the methyl-orange method.

## Results

*Single-dose Studies.*—The observed concentrations of pempidine in plasma after a single oral dose are summarized in Table I. This demonstrates a striking consistency in the measurements which made it possible to predict quite accurately the amount of

TABLE I.—*Plasma Concentrations of Pempidine in mμg./ml. for Six Hours After a Single Oral Dose*

| Case No. | Pempidine Dose (mg.) | Form of Dose | Hours After Dose | | | | |
|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | 2 | 4 | 6 |
| 1 | 10 | Tablet | 0 | 30 | 53 | — | 3 |
| 2 | 10 | ,, | 0 | 26 | 47 | — | 6 |
| 3 | 10 | ,, | 0 | 30 | 59 | 35 | 3 |
| 4 | 10 | ,, | 0 | 28 | 58 | 26 | 7 |
| 5 | 5 | ,, | 0 | 17 | 32 | — | 3 |
| 6 | 5 | ,, | 0 | 15 | 29 | 12 | 4 |
| 7 | 2·5 | ,, | 0 | 7 | 16 | 7 | 2 |
| 8 | 2·5 | ,, | 0 | 9 | 18 | 8 | 2 |
| 9 | 5 | Solution | 0 | 20 | 53 | 19 | 2 |
| 10 | 2·5 | ,, | 0 | 11 | 20 | 8 | 1 |

pempidine in plasma at any time after a stated dose. After a single oral dose the plasma concentration of pempidine increased rapidly to a maximum in about two hours, after which it fell to a very low value within six hours. The hypotensive response showed a similar variation with time (Fig. 1). The peak value of the pempidine concentration was proportional to the dose (Fig. 2). In two cases 20% and 22% of the dose was excreted in the urine during the first six hours, whereas only 11% was recovered from a third patient who had impaired renal function and a blood urea of 61 mg./100 ml. When the drug was administered in aqueous solution the general shape of the response curve was unaltered, but slightly higher plasma concentrations of pempidine were obtained than when it was given in tablet form (Table I).

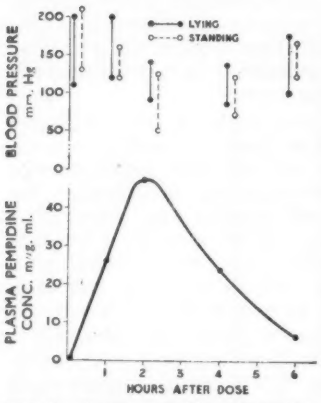



FIG. 1.—Plasma pempidine concentration and hypotensive response after a single 10-mg. oral dose in a previously untreated patient.

*Maintenance-dose Studies.*—With four daily doses of pempidine the peak values in plasma were higher than those found after a single dose (Table II). In addition, the response curve showed considerable broadening. In Fig. 3, curve *a* was obtained after a single 5-mg. dose of pempidine and curve *b* after stabilizing the same patient on a regime of 5 mg. four times daily. Again the plasma concentration increased with the amount of drug given, though the correlation was not so striking as it was with single doses.

*Studies on Patients with Renal Failure.*—Two uraemic hypertensive patients (blood urea 240 and 250 mg./100 ml.) were studied for four and six days respectively after starting treatment with pempidine. Each received 2.5 mg. twice daily, and blood samples were taken after the morning dose. On this small dose there was no increase in the concentration of plasma pempidine from day to day.

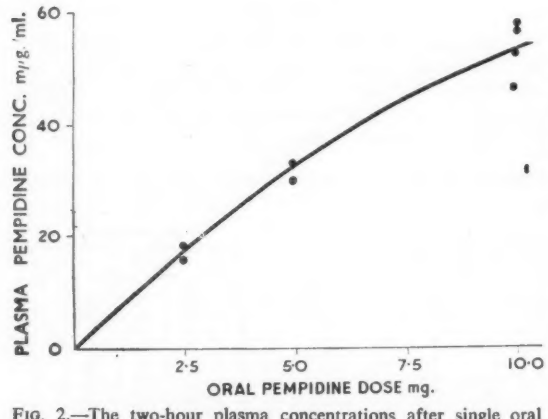



FIG. 2.—The two-hour plasma concentrations after single oral doses of pempidine in previously untreated patients.

TABLE II.—*Plasma Concentrations of Pempidine in mμg./ml. for Six Hours Following a Maintenance Dose*

| Case No. | Pempidine Dose (mg.) | Hours After Dose | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 4 | 6 |
| 11 | 25 | 115 | 192 | 237 | 204 | 127 |
| 12 | 10 | 5 | 48 | 68 | 52 | 14 |
| 13 | 10 | 0 | 21 | 51 | 23 | 2 |
| 14 | 5 | 3 | 24 | 33 | 27 | 5 |
| 15 | 5 | 3 | 30 | 49 | 27 | 1 |
| 16 | 2·5 | 0 | 8 | 30 | 15 | 2 |
| 17 | 2·5 | 0 | 7 | 31 | 8 | 3 |
| 18 | 2·5 | 3 | 11 | 30 | 13 | 4 |

*Studies on Out-patients.*—Using data from the maintenance-dose studies, standard curves were constructed so that a "predicted" value for the plasma pempidine concentration at the time of examination could be computed from the size and time of the last dose reported by the patients. Some patients were receiving chlorothiazide in addition to pempidine, and in such cases different standard curves were used to obtain the "predicted" concentrations, which are about two and a half times those for the same amounts of pempidine without chlorothiazide (Dollery *et al.*, in preparation). The "predicted" values were plotted against the values actually measured. Ideally, all the points should have fallen on the straight line shown in Fig. 4: in fact, 75% of the results were within ±50% of the predicted values, and these limits are indicated by the dotted lines. Only two patients (6%) had no pempidine in the plasma, and a further four (12%) had less than half the predicted value. Three patients (9%) had pempidine concentrations more than 50% higher than the predicted values; of these, two had impaired renal function with blood ureas of over 50 mg./100 ml.

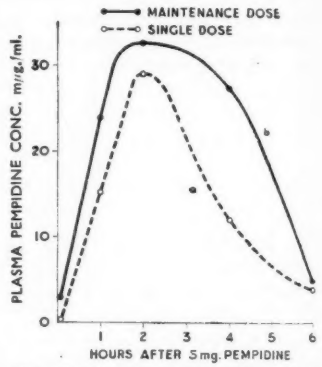



FIG. 3.—Plasma concentrations after a 5-mg. oral dose of pempidine given (*a*) as a first dose, and (*b*) as a six-hourly maintenance dose.

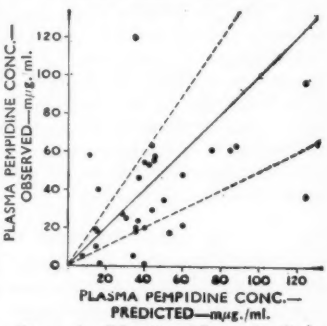



FIG. 4.—"Predicted" and "observed" values of plasma pempidine concentration in out-patients.

## Discussion

The dose/plasma-concentration relationship observed after single and multiple doses of pempidine is remarkably consistent, and this may well be the most important reason why the drug is so satisfactory in practice. Only if a drug has a constant, and therefore predictable, effect is it possible to achieve the delicate balance between inadequate control of blood-pressure and troublesome hypotension that is so necessary for

successful treatment. The results suggest that the hypotensive response to pempidine when given alone runs parallel to the plasma concentration rather than to the total amount in the body; for, despite the fact that the hypotensive response is small and the plasma concentration negligible six hours after an oral dose of pempidine, more than 75% of the dose must still be in the body, because there is no evidence that the drug is metabolized.

Work on rats (Harington *et al.*, 1958; Muggleton and Reading, 1959) has shown that pempidine is concentrated in liver, kidney, and spleen, and it is reasonable to suppose that this may also apply in man. After oral administration of pempidine three processes will account for the characteristic shapes of the response curves obtained with isolated and maintenance doses. These are (1) absorption of the drug, (2) passage into the tissues, and (3) renal excretion. For a single dose the peak of the curve is sharp and the steep falling limb represents loss of drug from the blood by both (2) and (3) because the tissues initially contain no pempidine. With a maintenance dose, however, the curve is broader and initially less steep because the tissues already contain pempidine, so that (2) is relatively unimportant and (3) alone is largely responsible for removal of drug from the blood.

The two uraemic patients were given pempidine twice instead of four times a day. In one of them the peak plasma concentration of pempidine after 2.5 mg. was the same (30 mμg./ml.) as that found in patients with a normal renal function after the same dose. The plasma concentrations showed no tendency to rise from day to day, and, despite the severe impairment of renal function, there was no evidence of pempidine accumulating in the body.

Three-quarters of the out-patients had plasma concentrations of pempidine within ±50% of the expected value, many of the values being much closer. Only two patients had no pempidine in their blood, and one of these had a satisfactory level at a later examination. The sample may be unavoidably biased, since patients may be more inclined to take their doses of pempidine before attending the clinic than at any other times, knowing that a satisfactory pressure, with a good postural effect on standing, wins approval. In several cases where blood-pressure control was not satisfactory a low plasma pempidine concentration was expected, but this did not prove to be the case. Such instances of escape from drug control are known to occur from time to time.

The conscientiousness of patients on long-term regimes of treatment is an important problem of present-day medicine. Other studies, most notably with *para*-aminosalicylic acid in the treatment of tuberculosis, have suggested a greater tendency to depart from the prescribed dose regimes than was indicated by our results. Indeed, Dixon *et al.* (1957) concluded that less than half of their tuberculous patients who were supposed to be taking *para*-aminosalicylic acid were in fact excreting it in their urine. Many factors must play a part: the bulk and side-effects of the drug, the severity of symptoms before treatment, and, perhaps most important of all, the patient's attitude to his disease. Our results show a gratifying degree of co-operation by the patients. It must be remembered, however, that all had severe symptoms of hypertension before treatment; they were therefore probably more conscientious than patients with only mild hypertension, who are less willing to accept the unpleasant side-effects of ganglion blockage. Careful follow-up in a special clinic where the patients always see the same doctors may also help to create a feeling of mutual trust.

**Summary**

A new sensitive method of estimation has allowed the measurement of plasma pempidine concentrations over the whole range of dosage used in practice. The plasma concentration, which was remarkably predictable for a given dose, was found to be closely related to the fall in blood-pressure on standing. Data from patients in hospital have been used to predict the plasma concentrations of the drug in out-patients: 75% were found to have concentrations within ±50% of the expected values, suggesting reasonably good co-operation by the patients.

We gratefully acknowledge the valuable technical assistance given by Mr. A. F. Ivens, who carried out the fluorescence measurements. Thanks are due also to Dr. H. W. Reading, who examined the urine samples, and to Dr. H. Campbell and Professor J. McMichael, F.R.S., for their interest and support.

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# CHLOROTHIAZIDE IN TREATMENT OF HIGH BLOOD-PRESSURE

## RESULTS OF A CONTROLLED TRIAL

BY

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Chlorothiazide has been stated by many observers to enhance the effects of a number of agents used in the treatment of patients with hypertension. Others have found that it reduced the blood-pressure when given by itself. A controlled trial of its effect when used with ganglion-blocking agents has not been carried out, nor, at the time when this work was started, had such a trial been carried out in which chlorothiazide was used alone. We present the results of a double-blind trial of the effect of chlorothiazide used both with ganglion-blocking drugs and alone in the treatment of high blood-pressure. Ganglion-blocking agents produce side-effects which are noticed by the patient and are reported to the observer. This difficulty is commonly held to invalidate an attempt at a controlled trial of these drugs, but in the group of patients here presented it proved not to be of importance.

### Methods

Seventeen patients with essential hypertension, of whom 10 were being treated with mecamylamine and

seven with pentolinium, were chosen for the trial. They lived close enough to the hospital to be able to attend once a week without inconvenience. Two patients were later withdrawn; the particulars of the remaining 15 are given in Table I.

TABLE I.—*Sex, Age, Blood-pressure Before any Treatment, and Duration of Preceding Treatment of Patients Used in Present Trial*

| Case | Sex and Age | B.P. Before Treatment | Duration of Treatment (Years) | Neuro-retinopathy Before Treatment |
|---|---|---|---|---|
| 1 | M 55 | 222/130 | 2½ | − |
| 2 | M 46 | 180/125 | 1 | − |
| 3 | M 55 | 200/120 | ½ | − |
| 4 | F 48 | 240/120 | 5 | − |
| 5 | M 48 | 280/150 | 1 | − |
| 6 | F 47 | 220/140 | 1 | − |
| 7 | F 59 | 270/130 | 1 | − |
| 8 | M 57 | 225/125 | 2½ | − |
| 9 | F 36 | 220/130 | 3 | − |
| 10 | M 49 | 210/140 | 5 | − |
| 11 | F 48 | 300/160 | 4 | + |
| 12 | M 51 | 210/130 | 3 | + |
| 13 | F 44 | 240/135 | 5 | + |
| 14 | M 53 | 230/130 | 4 | − |
| 15 | F 53 | 235 135 | 5 | + |

The trial lasted for 24 weeks. Each patient, for six weeks at a time, received one of four combinations of tablets. These were: (1) ganglion-blocker plus chlorothiazide; (2) ganglion-blocker plus dummy chlorothiazide; (3) dummy ganglion-blocker plus chlorothiazide; (4) dummy ganglion-blocker plus dummy chlorothiazide. Except that dummy ganglion-blocker was not given for any two successive periods, the order of treatment was random, and was not known to us until the trial was finished. No alteration was made in the diet of any patient.

In addition, and throughout the 24 weeks, each patient received supplementary potassium, initially in the form of 3 g. of potassium chloride as enteric-coated tablets. Later, when it was discovered that one patient was passing these unchanged per rectum, and when other patients were showing low levels of potassium in their plasma, a mixture of potassium chloride, potassium bicarbonate, and potassium acetate in water was given, so that each patient received a supplement of approximately 66 mEq of potassium daily.

The patients were seen once weekly, when the blood-pressures were taken twice in the standing and lying position and the averages for each posture were recorded. Blood samples for the estimation of plasma potassium were taken approximately once a month.

The interval between the last dose of tablets and the measurement of blood-pressure was not the same for all patients. Therefore, though each patient was seen each week at approximately the same time after his last dose of drugs, there was considerable variation in this interval between one patient and another.

Chlorothiazide was given in a dose of 250 mg. three times daily. Since it was unnecessary for our purpose, no attempt was made to give the patients the maximum tolerable dose of ganglion-blocking drug. The dose was not changed from that given before the trial began, except in special circumstances. It was decided that patients should be allowed to reduce the dose of ganglion-blocking agent, or of its dummy, if any started to experience troublesome symptoms of hypotension at any time. Conversely, if during any period the patient developed evidence of hypertensive neuroretinopathy or a consistently very high diastolic blood-pressure, the dose of presumed ganglion-blocker should be increased. If this produced no fall in blood-pressure, the patient received the drug-combination schedule for the next period of the trial and took this for the ensuing six weeks.

### Significance of Side-effects

At the beginning of the trial all patients were told that at some time they might experience dizziness, particularly on standing up, and they were asked to reduce their dose of presumed ganglion-blocking drug if this occurred. They were reminded of this at the beginning of each six-weeks period. No patient was asked about symptoms that might have been due to parasympathetic ganglion blockade, but a number volunteered such information. An analysis of symptoms reported by the patients is given in Table II, which shows how difficult it would have been to deduce from these reports whether or not a patient was taking active or dummy ganglion-blocker at the time.

TABLE II.—*Occurrence of Reported Side-effects During Treatment with Active and Dummy Ganglion-blocking Agents*

| | Ganglion-blocker Reduced Because of Orthostatic Dizziness | Dizziness, Ganglion-blocker Not Reduced | Dryness of Mouth | Blurred Vision | Constipation |
|---|---|---|---|---|---|
| No. of patients on active blocker | Mecamylamine, 4<br>Pentolinium, 4 | 1 | 1 | 0 | 2 |
| No. of patients on dummy blockers | Mecamylamine, 4<br>Pentolinium, 2 | 1 | 1 | 3 | 1 |

The blood-pressure was recorded as lower than the mean control value for each patient on six of the nine occasions when orthostatic dizziness was reported by patients taking active blocking agents: it was not observed to differ from the mean control value in any of the seven patients taking dummy blocker except in two, who were taking active chlorothiazide. A fall in blood-pressure was recorded on all occasions when patients taking active ganglion-blocker reported symptoms of parasympathetic ganglion blockade: it was recorded in none of the five patients who reported these symptoms when taking dummy ganglion-blocking drugs.

*Patients Taking Two Dummy Tablets.*—After three weeks on this treatment, one patient (Case 4), whose blood-pressure had been consistently at a level of 210/138, developed a retinal haemorrhage, and she was accordingly given the next combination of drugs in her schedule (Table III). On the other hand, it is of interest that Cases 11, 12, 13, and 15 (Table IV), all of whom had had hypertensive neuroretinopathy some years previously, did not revert to high levels of blood-pressure.

*Patients Taking Mecamylamine.*—Of these 11 patients, one developed a generalized erythematous maculopapular rash after a few days on what was subsequently discovered to have been chlorothiazide. One patient of unstable temperament became convinced that chlorothiazide was exacerbating her emotional instability. These two patients were accordingly withdrawn from the trial. Table III shows that, in the remaining eight patients, mecamylamine when given alone produced a significant fall in the mean values of the standing systolic and diastolic blood-pressures for the group as a whole but no such change in the lying

blood-pressures. Of the individual patients, in six a significant fall in standing systolic blood-pressure was achieved, in four of whom the standing diastolic blood-pressure was significantly lowered. The systolic pressure in the lying position was lowered significantly in three patients and the diastolic pressure in one.

*When chlorothiazide was added to the mecamylamine* the mean fall for the group was much greater, and significant both for lying and for standing systolic and diastolic values. Of the individual patients, all showed a significant fall in their standing systolic and seven out of the eight in their standing diastolic blood-pressures. In the lying position, two failed to show a significant fall in the systolic pressure and three showed no such change in the diastolic pressure. One patient (Case 4) reduced the dose of mecamylamine from 75 mg. daily to 70 mg. Case 1 reduced the dose from 30 mg. to 22.5 mg.; Case 6 from 30 mg. to 7.5 mg.; and Case 7 from 35 mg. to 15 mg. daily, because of hypotensive episodes.

*Patients Taking Pentolinium.*—For reasons not apparent to us, the control values of the mean blood-pressure for each of these patients varied within much wider limits than did those of the group taking mecamylamine. There was no evidence that pentolinium alone in the doses being used caused a significant reduction in the blood-pressure of any one of these patients in either the standing or the lying position (Table IV).

*When Chlorothiazide was Added to Pentolinium.*—One patient (Case 14) showed a pronounced fall in blood-pressure. Case 13 also showed a large fall, but this was no greater than that obtained when chlorothiazide alone was used (Table V).

*Effect of Chlorothiazide Alone.*—It seemed unlikely that the response of any patient to chlorothiazide alone would be determined by the type of ganglion-blocking agent that they might have been taking in the period before. Accordingly, the results obtained in the two groups of patients are presented together. Table V shows that chlorothiazide reduced the mean standing systolic pressure for the group by an amount which was barely significant, whereas the reduction achieved in the standing diastolic blood-pressures was significant. In the lying position the reductions in systolic and diastolic pressures were less than in the standing position. The systolic pressure was not significantly altered and the diastolic was scarcely so. Out of the

TABLE III.—*Changes in Blood-pressure of Eight Patients when Taking Mecamylamine Alone and Mecamylamine Plus Chlorothiazide*

| Case | | Control Blood-pressure ±S.E. | | Fall in Blood-pressure | | | |
|---|---|---|---|---|---|---|---|
| | | | | On Mecamylamine Alone | | On Mecamylamine + Chlorothiazide | |
| | | Standing | Lying | Standing | Lying | Standing | Lying |
| 1 | Systolic | 178·0 ± 7·9 | 178·0 ± 10·6 | 16·4 | 7·7 | 55·4 | 25·9 |
| | Diastolic | 112·0 ± 6·8 | 108·0 ± 9·6 | 5·8 | 1·5 | 27·3 | 8·6 |
| 2 | Systolic | 175·8 ± 4·9 | 174·1 ± 6·7 | 11·8 | 16·1 | 35·8 | 25·6 |
| | Diastolic | 124·8 ± 4·4 | 117·6 ± 5·0 | 8·6 | 8·0 | 26·4 | 14·2 |
| 3 | Systolic | 159·3 ± 15·4 | 164·6 ± 1·6 | 40·5 | 16·3 | 45·6 | 25·6 |
| | Diastolic | 100·3 ± 8·8 | 96·0 ± 8·1 | 22·3 | 8·0 | 24·1 | 9·8 |
| 4 | Systolic | 210·0 ± 0·0* | 206·6 ± 5·6 | 29·0 | 27·6 | 68·7 | 45·8 |
| | Diastolic | 138·6 ± 2·9 | 132·6 ± 6·4 | 12·4 | 10·0 | 42·5 | 26·3 |
| 5 | Systolic | 194·1 ± 5·2 | 195·0 ± 12·2 | 53·5 | 33·0 | 64·1 | 34·0 |
| | Diastolic | 133·0 ± 3·6 | 126·6 ± 5·1 | 36·0 | 26·8 | 38·2 | 30·6 |
| 6 | Systolic | 163·0 ± 9·1 | 178·6 ± 5·5 | 20·0 | 1·6 | 32·0 | 21·6 |
| | Diastolic | 113·0 ± 3·0 | 114·0 ± 5·5 | 12·6 | −2·0 | 25·0 | 14·6 |
| 7 | Systolic | 210·6 ± 15·6 | 209·0 ± 16·0 | 9·8 | 0·7 | 48·1 | 30·7 |
| | Diastolic | 129·6 ± 7·6 | 127·2 ± 5·5 | 1·1 | −1·1 | 35·3 | 24·7 |
| 8 | Systolic | 168·0 ± 7·5 | 145·0 ± 10·0 | 5 | −22 | 27 | 3 |
| | Diastolic | 109·0 ± 7·4 | 92·0 ± 11·5 | 8 | −12 | 12·4 | 2 |
| Mean fall | Systolic | | | 23·2 ± 5·9 | 10·1 ± 6·1 | 47·0 ± 5·3 | 26·5 ± 4·2 |
| | Diastolic | | | 13·3 ± 3·9 | 4·9 ± 4·1 | 28·2 ± 3·4 | 16·4 ± 3·5 |

* Mean of three readings. In this and the following tables, a minus sign before a figure means that there was a rise in blood-pressure.

TABLE IV.—*Changes in Blood-pressure of Seven Patients when Taking Pentolinium Alone and Pentolinium Plus Chlorothiazide*

| Case | | Control Blood-pressure (±S.E.) | | Fall in Blood-pressure | | | |
|---|---|---|---|---|---|---|---|
| | | | | On Pentolinium Alone | | On Pentolinium + Chlorothiazide | |
| | | Standing | Lying | Standing | Lying | Standing | Lying |
| 9 | Systolic | 188·3 ± 6·0 | 185·0 ± 10·0 | −2 | −8·8 | 0·8 | −15·8 |
| | Diastolic | 114·6 ± 4·5 | 109·0 ± 8·0 | −4 | −9 | −4·7 | −6·3 |
| 10 | Systolic | 181·8 ± 26·6 | 179·6 ± 11·3 | 2·6 | −12 | −3·4 | −12·4 |
| | Diastolic | 136·2 ± 5·0 | 137·4 ± 7·5 | −6·8 | −9·2 | −1·2 | −0·6 |
| 11 | Systolic | 181·0 ± 16·4 | 193·0 ± 14·8 | 7 | 6 | −1 | 6·4 |
| | Diastolic | 112·8 ± 7·1 | 113·2 − 6·9 | 8·2 | 2·4 | 12·2 | 15 |
| 12 | Systolic | 180·8 ± 12·4 | 180·0 ± 11·4 | −3·4 | −19·2 | 16·7 | 5 |
| | Diastolic | 114·3 ± 6·4 | 113·8 ± 8·0 | 0·8 | −10·9 | 8 | 2·2 |
| 13 | Systolic | 185·0 ± 27·2 | 194·6 ± 10·8 | 3·7 | 8 | 52 | 42·6 |
| | Diastolic | 119·6 ± 11·6 | 120·5 ± 15·7 | 5·8 | 12·4 | 34·6 | 31·5 |
| 14 | Systolic | 158·3 ± 19·7 | 181·6 ± 27·3 | 26·2 | 19·1 | 62·3 | 47·6 |
| | Diastolic | 95·0 ± 16·5 | 112·1 ± 11·2 | −2·4 | −6·7 | 21 | 27·5 |
| 15 | Systolic | 185·0 ± 18·7 | 192·1 ± 25·7 | −4·6 | −19·5 | 15 | 18·1 |
| | Diastolic | 112·6 ± 10·9 | 107·5 ± 11·5 | 4·1 | 2 | 14·6 | 10·9 |
| Mean fall | Systolic | | | 4·2 ± 4·0 | −3·7 ± 5·7 | 20·3 ± 10·1 | 13·0 ± 9·4 |
| | Diastolic | | | 0·4 ± 2·2 | −2·7 ± 3·2 | 12·0 ± 5·0 | 11·4 ± 5·3 |

TABLE V.—*Changes in Blood-pressure of 15 Patients Taking Chlorothiazide Alone*

| Case | | Control Blood-pressure (±S.E.) | | Fall in Blood-pressure on Chlorothiazide Only | |
|---|---|---|---|---|---|
| | | Standing | Lying | Standing | Lying |
| 1 | Systolic .. | 178·0± 7·9 | 178·0±10·6 | 1·4 | 6·4 |
| | Diastolic | 112·0± 6·8 | 108·0± 9·6 | 5·6 | 0·3 |
| 2 | Systolic .. | 175·8± 4·9 | 174·1± 6·7 | 19·8 | 8·1 |
| | Diastolic | 124·8± 4·4 | 117·6± 5·0 | 16·2 | 4·0 |
| 3 | Systolic .. | 159·3±15·4 | 164·6±16·0 | 7·5 | 4·2 |
| | Diastolic | 100·3± 8·8 | 96·0± 8·1 | 2·7 | 4·2 |
| 4 | Systolic .. | 210·0± 0·0* | 206·0± 5·8 | 63·7 | 47·9 |
| | Diastolic | 138·6± 2·9 | 132·6± 6·4 | 35·0 | 27·4 |
| 5 | Systolic .. | 194·1± 5·2 | 195·0±12·2 | 27·1 | 9·0 |
| | Diastolic | 133·0± 3·6 | 126·6± 5·1 | 15·2 | 13·8 |
| 6 | Systolic .. | 163·0± 9·1 | 178·6± 5·5 | 22·9 | 29·0 |
| | Diastolic | 113·0± 3·0 | 114·0± 5·5 | 16·6 | 11·7 |
| 7 | Systolic .. | 210·6±15·6 | 209·0±16·0 | −22·4 | −15·0 |
| | Diastolic | 129·6± 7·6 | 127·2± 5·5 | −1·0 | −2·4 |
| 8 | Systolic .. | 168·0± 7·5 | 145·0±10·0 | 20·0 | −3·8 |
| | Diastolic | 109·0± 7·4 | 92·0±11·5 | 10·0 | −1·0 |
| 9 | Systolic .. | 188·3± 6·0 | 185·0±10·0 | −13·7 | −23·0 |
| | Diastolic | 114·6± 4·5 | 109·0± 8·0 | −3·2 | −8·2 |
| 10 | Systolic .. | 181·8±26·6 | 179·6±11·3 | −17·4 | −7·0 |
| | Diastolic | 136·2± 5·0 | 137·4± 7·5 | −3·5 | −3·1 |
| 11 | Systolic .. | 181·0±16·4 | 193·0±14·8 | −14·0 | −3·7 |
| | Diastolic | 112·8± 7·1 | 113·2± 6·9 | 2·3 | 1·6 |
| 12 | Systolic .. | 180·8±12·4 | 180·0±11·4 | 7·8 | −13·3 |
| | Diastolic | 114·3± 6·4 | 113·8± 8·0 | 4·1 | −3·7 |
| 13 | Systolic .. | 185·0±27·2 | 194·6±10·8 | 51·7 | 37·1 |
| | Diastolic | 119·6±11·6 | 120·5±15·7 | 28·8 | 18·9 |
| 14 | Systolic .. | 158·3±19·7 | 181·6±27·3 | 36·7 | 34·1 |
| | Diastolic | 95·0±16·3 | 112·1±11·2 | 9·4 | 14·6 |
| 15 | Systolic .. | 185·0±18·7 | 192·1±25·7 | 6·1 | −11·2 |
| | Diastolic | 112·6±10·9 | 107·5±11·5 | 8·8 | 2·5 |
| Mean fall .. | Systolic .. | | | 13·2±6·5 | 6·5±5·5 |
| | Diastolic | | | 9·8±2·9 | 5·3±2·5 |

* Mean of three readings.

15 patients five (Cases 2, 4, 5, 6, and 13) showed a marked fall in their blood-pressure. In Case 4 the reduction in blood-pressure produced by chlorothiazide was almost as great as when this drug was combined with mecamylamine. Of these five patients, all except Case 6 showed a greater fall in systolic blood-pressure when standing than when lying. A similar postural difference in the diastolic blood-pressure was shown by all.

### Relationship of Time Interval Between Last Dose of a Drug and Change in Blood-pressure

No attempt was made to ensure that all the patients took their drugs at the same time before their blood-pressure was recorded, though for each individual patient the interval between taking the tablets and attendance at the clinic remained approximately the same throughout the trial. Since this interval was an uncontrolled variable that might have affected our observations, it seemed of interest to see whether there was any relationship between it and changes in the blood-pressure.

The time that had elapsed since the last dose of drugs was recorded each time the blood-pressure was observed; the time was ascertained for all the patients when they were taking ganglion-blocking agents, but for only 9 of the 15 patients when they were taking chlorothiazide alone. For each patient the average interval was calculated for each of the three periods when active drugs were taken, together with the difference between the average standing systolic blood-pressure in the control period and each of the other periods. The two values were plotted against one another and regression lines were calculated. The results of these calculations were significant only for the period when chlorothiazide was used alone. The Chart shows the regression line obtained, the slope of which is significant ($0.02<P<0.05$). Between two and six hours after the last dose of chlorothiazide the fall in systolic blood-pressure in the standing position is progressively greater.

### Discussion

In a controlled trial it must be shown that the observations of the investigator have not been invalidated by a knowledge of what substances were being prescribed at any one time. In this trial, knowledge of the patients' plasma potassium levels and of the side-effects produced by mecamylamine and pentolinium could both have influenced the figures which we recorded as the patients' blood-pressures. In three patients, of whom only one was found to have a reduced blood-pressure when taking chlorothiazide alone, low potassium levels led us to suppose that chlorothiazide was being used during the first two weeks of the trial. After this a solution of mixed potassium salts was substituted for enteric-coated tablets of potassium chloride, and no patient was found to have a low plasma potassium level subsequently.

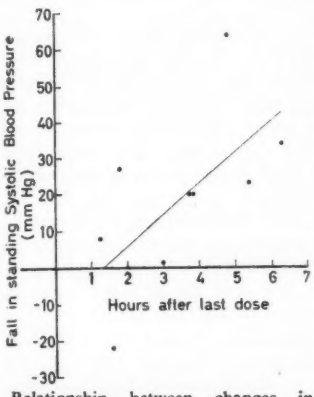
The possible influence of the patients' complaints of side-effects from mecamylamine and pentolinium is a much more important and interesting point. It had always seemed to us that the method of the double-blind trial was not suitable for assessing the effects of substances that produced symptoms in the patient, since the observations of the investigator would be influenced if the patient mentioned his symptoms. This argument seemed particularly cogent in the case of the ganglion-blocking drugs, which produce symptoms so unpleasant that the physician cannot remain unaware of them. In fact, the patients in this trial made complaints suggesting the side-effects of mecamylamine or pentolinium more often when they were taking dummy ganglion-blocking tablets than when they were taking the real drugs. Chlorothiazide cannot have been responsible for this, since only two patients were taking it when these symptoms were reported.

It can be objected that, had an effective dose of pentolinium been used, symptoms would have been reported more often when active ganglion-blockers were given. But, though mecamylamine treatment was effective in all the patients concerned, the dose of active tablets was reduced no more frequently than that of the dummy tablets. An analysis of the blood-pressure readings at the time of these complaints shows that on no occasion was a reduction in blood-pressure observed when neither active ganglion-blocker nor active chlorothiazide was being taken, and that such a reduction was not always seen when one or both of these substances were being used. Thus there was no evidence that the patients' reports of side-effects influenced our measurements of their blood-pressure. It is clear, therefore, that it is possible to conduct a double-blind trial of ganglion-blocking agents, at least in a group of patients who have already been treated with them for some time, and when the active or dummy tablets are used for a succession of short periods.

Hall and Owen (1959), in a controlled trial, found that chlorothiazide reduced the blood-pressure of hypertensive patients when used alone. The present investigation, which was begun before their report was published, confirms their conclusion and shows that in 5 out of 15 patients chlorothiazide alone produced

considerable falls in blood-pressure. In two patients (Cases 4 and 13) no extra effect was produced by the addition of a ganglion-blocking drug. Case 4 had a grossly raised blood-pressure during the time she was receiving two dummies and developed a retinal haemorrhage within three weeks. The usefulness of chlorothiazide is therefore not confined to patients with only moderate degrees of hypertension.

The Chart shows the correlation between the time that had elapsed since the last dose of chlorothiazide alone and the reduction in the standing systolic blood-pressure. A relationship of this kind may vitiate the results of any trial in which blood-pressure is recorded infrequently. In this instance there was an even distribution of times between dosage and blood-pressure measurement, so that the results may be representative of the effect of chlorothiazide alone.




Relationship between changes in standing systolic blood-pressure and the time since the last dose of chlorothiazide in nine patients.

There was no evidence that the arterial pressure was affected in patients taking pentolinium alone. In all but one the initial arterial pressure, three to five years previously, was much higher than that recorded in the control period of the present trial, and four of them (Cases 11, 12, 13, and 15) presented with hypertensive neuroretinopathy. It is impossible, on the available evidence, to prove that this reduction in blood-pressure was due to the drugs used. But, if it were so, the question would arise whether such treatment, for a limited period, may not effect a remission in the course of the disease.

### Summary

It has been shown that is is possible to carry out a double-blind controlled trial of ganglion-blocking agents, since the incidence of side-effects was no less when dummy tablets were used than when active drugs were employed. Reports of side-effects by the patients did not influence the readings of the blood-pressure.

Chlorothiazide produced a significant fall of blood-pressure in 5 out of 15 patients when given alone in a dose of 250 mg. three times daily.

Chlorothiazide enhanced the reduction of blood-pressure achieved by mecamylamine in all of eight patients, and increased the effect of pentolinium in one of seven patients.

Our thanks are due to Professor Sir George Pickering for his criticism and advice, to Miss Susan Partridge and Miss Joyce Hollobon for their help in the clinic, and to the pharmaceutical department for dispensing the tablets. We also acknowledge with gratitude the supply of inert tablets by Messrs. May & Baker and Messrs. Merck Sharp and Dohme.

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# RELATIVE ANTIBACTERIAL ACTIVITY OF THREE PENICILLINS

BY

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A new oral penicillin, the potassium salt of 6-(alpha-phenoxypropionamido) penicillanic acid, has recently been marketed in this country under the name "broxil." The only published information about it relates to its absorption, which is claimed to be much more nearly complete than that of phenoxymethylpenicillin (penicillin V); the blood levels attained are about double those produced by the same dose of penicillin V, and equivalent to those produced by an intramuscular injection of the same dose of benzylpenicillin (penicillin G) (Knudsen and Rolinson, 1959). Information about its antibacterial activity was communicated to the Seventh Annual Antibiotics Symposium in Washington in November last, but is not yet in print. Some of this information suggested a superior action against penicillin-resistant staphylococci, apparently owing to its slower inactivation by penicillinase (Report, 1959).

Since broxil, which is referred to here as penicillin B, is recommended for use in a wide variety of infections, further assessment of its activity against not only staphylococci but other bacteria is evidently called for, and the following preliminary observations were made with this object. Comparison was made with penicillins G and V. It is known that these two are not identical in activity. G is more active against streptococci and V against some staphylococci, but differences hitherto recorded have been only of the order of twofold (Martin, Nichols, and Heilman, 1955; Zischka, 1956; Lund, 1957).

### Methods

The plate-dilution method, with a dilute inoculum, described by Garrod and Waterworth (1956), was used for all species, the medium being nutrient agar for non-exacting species, with the addition of saponin-lysed horse blood for *Str. pyogenes* and *Str. pneumoniae*, and "chocolate" agar for *H. influenzae*. The inoculated areas were separated by ditches in tests of *Proteus*.

A second series of tests was done with penicillin-resistant strains of *Staph. pyogenes*, 2.5 ml. of broth containing concentrations of penicillin falling by four-fold from 512 μg./ml. being inoculated with one 0.02-ml. drop of undiluted broth culture and read for presence or absence of turbidity after 18 hours. When this large inoculum is used the result is determined by whether preformed penicillinase in the inoculum, the amount of which varies greatly between different strains, can destroy the penicillin before it exerts its bactericidal effect. Penicillin-sensitive strains of this organism were also tested by this method, the concentrations falling by twofold from 0.12 μg./ml.

All the organisms used were recently isolated from clinical material except some strains of *Str. pyogenes* and *Str. pneumoniae*.

### Results

*Staph. Pyogenes.* — The findings obtained with sensitive strains were so uniform as only to require description in general terms. In the plate-dilution test

each of 36 strains was inhibited by either 0.015, 0.03, or 0.06 μg./ml. of all three forms of penicillin, and there was never more than a difference of one tube between them for any one strain. For what differences of one tube are worth, 1 strain was most sensitive to G, 12 were most sensitive to V, 2 more sensitive to V and B than to G, and 10 more sensitive to V and G than to B, while 11 were equally sensitive to all three. Repetitions of these tests by the tube-dilution method gave similar results. Resistant (penicillinase-forming) strains likewise showed only differences of one tube in sensitivity to the three penicillins in the plate-dilution test, and, with the small inoculum used for this, nearly all the inhibitory concentrations were <1 μg./ml. A very different picture is produced by the tube-dilution test with a large inoculum. The results obtained with this are given in Table I, the 38 strains being graded

TABLE I.—*Minimum Inhibitory Concentrations of Three Penicillins for Resistant Staphylococci (Tube-dilution Test With Heavy Inoculum)*

| No. of Strains | M.I.C. (μg./ml.) | | | No. of Strains | M.I.C. (μg./ml.) | | |
|---|---|---|---|---|---|---|---|
| | G | V | B | | G | V | B |
| 2 | 0·5 | 0·12 | 0·03 | 3 | 32 | 8 | 2 |
| 1 | 0·5 | 0·5 | 0·12 | 1 | 32 | 32 | 0·5 |
| 1 | 2 | 0·12 | 0·12 | 1 | 32 | 32 | 2 |
| 1 | 2 | 0·12 | 0·5 | 1 | 32 | 32 | 8 |
| 1 | 2 | 0·5 | 0·12 | 1 | 128 | 32 | 0·5 |
| 3 | 2 | 0·5 | 0·5 | 1 | 128 | 32 | 8 |
| 1 | 8 | 0·03 | 0·12 | 1 | 128 | 128 | 8 |
| 2 | 8 | 0·12 | 0·12 | 1 | 128 | 512 | 32 |
| 1 | 8 | 0·12 | 0·5 | 1 | 512 | 128 | 8 |
| 2 | 8 | 0·5 | 0·5 | 2 | 512 | 512 | 32 |
| 3 | 8 | 2 | 0·5 | 1 | 512 | >512 | 32 |
| 1 | 32 | 0·5 | 0·5 | 1 | >512 | 512 | 32 |
| 1 | 32 | 2 | 0·12 | 1 | >512 | 512 | 128 |
| 2 | 32 | 8 | 0·5 | | | | |

in order of diminishing sensitivity to G. The first eight produce so little penicillinase that they are reasonably sensitive to all three penicillins, and the last nine so much that they are too resistant to all of them for therapy of any such infection to have any prospect of success. Without exception they are more sensitive to V or B than to G, and these differences are very large among strains of intermediate degrees of resistance to G, amounting in several instances to 256-fold. Many are considerably more sensitive to B than to V, though in a few strains this position is reversed.

*Streptococci.* — The order of activity against *Str. pyogenes* (group A), *Str. faecalis*, and *Str. pneumoniae* (pneumococcus) is consistently G>V >B, (Table II), but the differences are not great, being only twofold—where they exist—between G and V, and at maximum fourfold between G and B.

*Gram-negative Bacilli* (Table III).—Two species less resistant to penicillin than most other Gram-negative

TABLE II.—*Minimum Inhibitory Concentrations of Three Penicillins for Three Species of Streptococci*

| | No. of Strains | M.I.C. (μg./ml.) | | |
|---|---|---|---|---|
| | | G | V | B |
| *Str. pyogenes* (11 strains) | 4 | 0·007 | 0·007 | 0·03 |
| | 5 | 0·007 | 0·015 | 0·03 |
| | 1 | 0·015 | 0·015 | 0·03 |
| | 1 | 0·03 | 0·03 | 0·06 |
| *Str. faecalis* (11 strains) | 1 | 1 | 1 | 2 |
| | 2 | 2 | 2 | 4 |
| | 8 | 2 | 4 | 4 |
| *Str. pneumoniae* (12 strains) | 3 | 0·015 | 0·015 | 0·03 |
| | 1 | 0·015 | 0·015 | 0·06 |
| | 3 | 0·015 | 0·03 | 0·03 |
| | 4 | 0·015 | 0·03 | 0·06 |
| | 1 | 0·03 | 0·03 | 0·06 |

TABLE III.—*Minimum Inhibitory Concentrations of Three Penicillins for Two Species of Gram-negative Bacilli*

| | No. of Strains | M.I.C. (μg./ml.) | | |
|---|---|---|---|---|
| | | G | V | B |
| *H. influenzae* (7 strains) | 1 | 0·25 | 2 | 2 |
| | 1 | 0·25 | 2 | 4 |
| | 1 | 0·5 | 2 | 8 |
| | 2 | 0·5 | 4 | 4 |
| | 1 | 1 | 4 | 2 |
| | 1 | 1 | 16 | 32 |
| *Proteus mirabilis* (10 strains) | 2 | 4 | 32 | 256 |
| | 2 | 4 | 64 | 256 |
| | 1 | 4 | 64 | 512 |
| | 2 | 8 | 128 | 512 |
| | 1 | 8 | 128 | >512 |
| | 2 | 16 | 128 | >512 |

bacilli were examined. *H. influenzae* is very much more sensitive to G than to V, the difference being usually eightfold, and B has the same order of activity as V. *Proteus* was examined because treatment with penicillin V, in dosage which, according to the result of a sensitivity test (with G), should have been fully effective, had not been entirely successful in preventing the recurrence of a urinary infection due to this organism. The 10 strains in Table III are *P. mirabilis*; one of *P. vulgaris* behaved similarly and one of *P. rettgeri* quite differently. Against this organism G is 8–16 times as active as V, and 64 or more times as active as B.

## Discussion

These observations reveal considerable differences in antibacterial activity *in vitro* between the new penicillin (B) and penicillin G. They also show greater differences between the activities of penicillins G and V than have hitherto been generally recognized. They might with advantage be extended to other species. The existence of such differences raises the question whether sensitivity tests performed as a guide to treatment can continue to be carried out solely with penicillin G, as at present. When another penicillin may or may not be many times more active, a further test with it may seem to be called for, at least in a difficult or critical case. In testing staphylococci, the degree of penicillin resistance of which varies so greatly, some such standard as that proposed by Abboud and Waisbren (1959) may be found helpful.

In so far as *in vitro* tests are an indication of therapeutic activity, the following conclusions may be drawn. B is decidedly the penicillin of choice for treating resistant staphylococcal infections, and might indeed be preferred for all such infections when facilities are not readily available for determining whether they are resistant or not. It is somewhat less active than G against streptococci and pneumococci, but the higher blood levels attained may compensate for this. It has a relatively very poor activity against the two Gram-negative species tested, and is to that extent less likely to be effective in bronchial and urinary-tract infections.

## Summary

A comparison has been made between the antibacterial activity *in vitro* of benzylpenicillin (G), phenoxymethylpenicillin (V), and the potassium salt of 6-(alpha-phenoxypropionamido) penicillanic acid (B).

The usual order of activity against penicillin-resistant staphylococci, in a form of test which measures resistance to penicillinase, is B>V>G, with wide differences.

The order against streptococci and pneumococci is G>V>B, with only small differences.

The order against *H. influenzae* and *Proteus* is also G>V>B, with considerable differences between G and the other two.

For the skilful and rapid execution of this work, and for devising the method used for resistant staphylococci, I am indebted to Miss Pamela M. Waterworth. I am also indebted to Beecham Research Laboratories Ltd. for a supply of "broxil," and to Dr. J. S. Murrell for many strains of staphylococci isolated during a current study of antibiotic resistance in septic lesions in out-patients.

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# ANTERIOR PITUITARY DEFICIENCY IN DISORDERS ASSOCIATED WITH STEATORRHOEA

BY

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Intestinal absorption may be impaired by a variety of disorders which, despite their diversity, often evoke a pattern of symptoms and signs which conforms to a characteristic clinical picture. Furthermore, these patients have a number of features in common with those of Addison's disease (Salvesen, 1956; Cooke and French, 1958). Prominent among these similarities are asthenia, pigmentation, intermittent diarrhoea, disturbances of water and sugar metabolism, disordered gastric secretory function, and the occurrence of macrocytic anaemia.

It is the purpose of this paper to show that defective intestinal absorption may be associated with decreased anterior pituitary activity and to relate this state to certain metabolic abnormalities which may occur in patients with steatorrhoea.

## Material

Seven female patients whose ages ranged from 16 to 64 years were studied; each had steatorrhoea with a 24-hour excretion of faecal fat which averaged 6 g. or more (Cooke, 1956). Two patients had idiopathic steatorrhoea, two had adult coeliac disease, one coeliac disease, one chronic relapsing pancreatitis, and one steatorrhoea following a partial gastrectomy (Table I).

All seven patients had clinical evidence, in varied degree, of endocrine deficiency; especially prominent were features reminiscent of Addison's disease. Investigations included estimation of the 24-hour urinary 17-ketosteroid excretion before and after corticotrophin administration, determination of the serum electrolyte and serum protein levels, examination of the peripheral blood and sternal marrow. With one exception (Case 2), routine urine tests for albumin and sugar were negative, and all had normal liver-function tests. Some patients were further investigated with water-loading and glucose-tolerance tests, a fractional test meal, and radioactive-iodine studies of thyroid function.

The influence of steroid therapy upon the water load and glucose-tolerance tests was studied in one patient (Case 1) over a period of five months. Water-loading tests were repeated four years later, when this patient reattended hospital, having ceased all therapy during the interval. In five patients the effect of treatment upon the blood-picture was also assessed.

## Assessment of Endocrine Activity

### Clinical Evidence

Pigmentation of the skin was present in five patients, three of whom had buccal pigmentation also. In one (Case 3) asthenia, abdominal discomfort, vomiting, and diarrhoea associated with extensive buccal pigmentation, and a low blood-pressure (100/50) would have justified a clinical diagnosis of Addison's disease.

A deficiency of both growth and gonadal stimulating hormones seemed probable in the youngest patient (Case 4), who had had coeliac disease since early childhood. She was physically retarded—height 53 in. (134.5 cm.), weight 65 lb. (29.5 kg.)—and lacked secondary sexual characteristics; her physical and bone age (assessed radiologically) were comparable with those of a girl aged 9, though her intelligence corresponded with her real age, 16 years.

The skin was smooth and atrophic in four patients; in one it had a semitranslucent appearance with an easily discernible vascular pattern. Some had fine "hair-lines" radiating from the angles of the mouth and eyes.

TABLE I.—*Patients with Intestinal Malabsorption*

| Case No. | Age | Diagnosis | Associated Conditions | Fat Excreted in Faeces in 24 Hours (g.) | Anaemia (Hb g. per 100 ml.) | Fasting Blood Sugar (mg./100 ml.) | Blood Electrolytes (mEq/l.) | | | | Blood Urea (mg./100 ml.) | Plasma Proteins (g./100 ml.) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Sodium | Potassium | Chlorides | Alkali Reserve | | Total | Alb. | Glob. |
| 1 | 47 | Adult coeliac disease | Bronchiectasis | 16 | Normocytic (11·3) | 30<br>57 | 147 | 4·4 | 102 | 36·0 | 32 | 6·5 | 3·4 | 3·1 |
| 2 | 54 | Chronic pancreatitis | Chronic nephritis | 6 | Macrocytic (6·8) | — | 144 | 5·9 | 112 | — | 77 | 6·5 | 4·2 | 2·3 |
| 3 | 26 | Idiopathic steatorrhoea | — | 6·5 | Macrocytic (5·3) | 95 | 140 | 5·1 | 100 | — | 45 | 6·8 | 4·4 | 2·4 |
| 4 | 16 | Coeliac disease | — | 14 | Normocytic (9·3) | 80 | 137 | 5·1 | 105 | 26·4 | 21 | 6·7 | 4·3 | 2·4 |
| 5 | 55 | Adult coeliac disease | Pulmonary sarcoidosis | 7·2 | Normocytic (13·3) | — | 140 | 5·0 | 103 | 28·3 | — | 6·9 | 4·3 | 2·6 |
| 6 | 64 | Idiopathic steatorrhoea | Diverticulitis. Prolonged thyroid medication (20 years) | 14 | Macrocytic (12·0) | — | 125 | 3·0 | 112 | — | 27 | 7·4 | 4·7 | 2·7 |
| 7 | 58 | Partial gastrectomy (1952) | — | 8·3 | Normocytic (12·9) | 83 | 130 | 4·9 | 102 | 30·0 | 30 | 6·7 | 4·9 | 1·8 |

TABLE II.—*Urinary 24-hour 17-ketosteroid Excretion (mg./day) Before and During Corticotrophin Administration in 7 Patients with Intestinal Malabsorption*

| | Case 1 | | | | | Case 2 | Case 3 | | | | Case 4 | | | Case 5 | Case 6 | | Case 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Before .. | <1 | <1 | <1 | — | 2·5† | 1·5 | <1 | 1·1 | <1 | 1·0 | 2·2 | <1 | <1 | 3·9 | 2·3 | 2 | 4·4 |
| During .. | — | — | 3·2 | 4·6* | 7·2† | 4·4 | — | — | — | 9·5 | — | 3·8 | 2·9 | 10·8 | — | — | 11·1 |

Urinary 17-ketosteroid excretion was reassessed during the last 24 hours of a three-day course of intramuscular corticotrophin 40 units thrice daily.
* After 2 weeks' administration of intramuscular corticotrophin 60 units twice daily.
† Re-estimation after interval of four years without treatment.

In three patients the absence of axillary hair was associated with sparse pubic hair and fine thinned scalp hair, but one (Case 2) had a masculine distribution of body hair with facial and limb hirsuties and a male type of baldness.

Five patients were post-menopausal. In one (Case 1), oligomenorrhoea preceded by nine years the onset of symptoms which coincided with the menopause at the age of 42; another (Case 2) was 39 when the menopause occurred, antedating symptoms by eight years. Emotional shock caused sudden cessation of menstruation in both patients. Of the two pre-menopausal patients, one (Case 4) had not menstruated, and the other (Case 3) had missed only one period.

### Investigations

*Urinary 17-Ketosteroid Excretion.*—The 24-hour urinary 17-ketosteroid excretion was measured (*a*) before treatment, (*b*) during the last 24 hours of a three-day course of intramuscular corticotrophin (Table II), and (*c*) after standard

TABLE III.—*Circulating Eosinophils Before and During Corticotrophin Administration*

| Case No. | Circulating Eosinophils/c.mm. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Days Before Corticotrophin | | | | During Corticotrophin | | | | |
| | 4 | 3 | 2 | 1 | 1 | 2 | 3 | 4 | 5 |
| 1 | 305 | 360 | 320 | 315 | 190 | 215 | 30 | 15 | 30 |
| 2 | — | — | 105 | 85 | 5 | 5 | — | — | — |

forms of treatment (Table IV). (*a*) All seven patients had subnormal steroid excretion levels and repeat estimations in four produced similar low values. (*b*) That these low steroid excretion levels were primarily due to anterior pituitary rather than adrenocortical deficiency was shown by the increased urinary steroid values during corticotrophin administration; one patient (Case 1) in whom corticotrophin therapy was continued had a further rise in 17-ketosteroid excretion after two weeks' treatment. Absolute eosinophil counts (Table III) before and during corticotrophin administration provided further evidence of adrenocortical responsiveness in two patients; a significant decrease in circulating eosinophils occurred, the response being immediate (within four hours) in Case 2 and delayed until the third day in Case 1. (*c*) Low steroid excretion levels persisted after two months' treatment with a gluten-free diet (Case 4), after administration of folic acid (Cases 2 and 4), and after vitamin $B_{12}$ therapy (Cases 3 and 6); neither the degree of anaemia nor body weight influenced the steroid excretion (Table IV).

*Serum Electrolytes.*—Serum electrolyte values were normal in all except two patients (Table I). In Case 6 the subnormal sodium (125 mEq/l.) and potassium (3 mEq/l.) levels were associated with considerable muscular weakness and were attributed to profuse diarrhoea, which had recurred intermittently for five months. Diarrhoea and weakness were in turn relieved or induced by giving or withholding oral potassium chloride therapy. Case 7 had a subnormal serum sodium level (130 mEq/l.).

*Diuretic Response to Oral Water-loading.*—The first part of the Robinson–Power–Kepler test was used as a standard oral water-load investigation in Cases 1, 2, 3, 6, and 7.

The patient was starved from 6 p.m., and all urine excreted between 10.30 p.m. and 7.30 a.m. was measured as the "night urine." After emptying the bladder at 8.30 a.m. the patient drank a quantity of water equivalent to 20 ml. per kg. body weight. At 9.30 a.m. and at hourly intervals until 12.30 p.m. the bladder was emptied; each hourly specimen was measured and the largest single hourly specimen noted as the "day urine."

In each of the five patients investigated the "day urine" failed to exceed in quantity the "night urine" (Table V). Case 2, however, had evidence of renal disease (albuminuria, and blood urea 77 mg./100 ml.), and in Case 6 the possibility of a renal tubular lesion could not be excluded owing to the presence of hypokalaemia (Cooke, 1957).

*Glucose-tolerance Test.*—Subnormal fasting blood-sugar levels were found in Case 1, but after oral glucose (50 g.) a satisfactory rise in blood sugar occurred (Table VI). Though normal blood-sugar curves were obtained in Cases 2, 3, and 4, the blood-sugar level failed to increase in Case 4 after oral glucose (Table VII).

*Thyroid Function.*—Radioactive iodine studies were made in two patients. They showed subnormal thyroid activity on two separate occasions in Case 1 and low normal activity in Case 2.

TABLE IV.—*Urinary 24-hour 17-ketosteroid Excretion in Relation to Age, Degree of Anaemia, Weight, Severity of Steatorrhoea, and Treatment*

| Case No. | Age | Urinary 17-Ketosteroids (mg./Day) | Haemoglobin % (g./100 ml.) | Weight lb. | Weight kg. | Faecal Fat (g./24 Hours) | Therapy |
|---|---|---|---|---|---|---|---|
| 1 | 47 | <1 | 67 (11·3) | 77 | 35·4 | 16 | Initially |
| | | <1 | 71 (10·5) | — | — | — | 2nd week — No specific therapy |
| | | <1 | — | 75 | 34·0 | — | 3rd " |
| | 51 | 2·5 | 77 (11·4) | 76 | 34·5 | 11 | 4 years later—no therapy during interval |
| 2 | 54 | 1·5 | 70 (10·4) | 158 | 71·7 | 6 | After 16 months' treatment with folic acid |
| 3 | 26 | <1 | 44 (6·5) | 96 | 43·5 | — | 3rd week |
| | | <1·1 | 68 (10·1) | 100 | 45·4 | — | 5th " — Vitamin $B_{12}$ |
| | | <1 | 89 (13·2) | 103 | 46·7 | 6·5 | 6th " — therapy |
| | | 1·0 | 100 (14·8) | 114 | 51·7 | — | 18th " |
| 4 | 16 | 2·2 | 63 (9·3) | 63 | 28·6 | 14 | Initially |
| | | <1 | 72 (10·6) | 65 | 29·5 | — | 4th week — No specific therapy |
| | | <1 | 95 (14·0) | 64 | 29·0 | — | After gluten-free diet for 2 months and folic acid therapy for 1 month |
| 5 | 55 | 3·9 | 90 (13·3) | 89 | 40·4 | 7·2 | Initial estimation. No specific therapy |
| 6 | 64 | 2·3 | 81 (12·0) | 91 | 41·3 | — | No specific therapy. After massive vitamin $B_{12}$ therapy for 6 weeks |
| | | 2·0 | 68 (10·1) | 98 | 44·5 | 14 | |
| 7 | 58 | 4·4 | 87 (12·9) | 95 | 43·1 | 8·3 | Initial estimation. No specific therapy |

TABLE V.—*Patients with Steatorrhoea. Impaired Water Excretion Following Oral Water Loading*

| Case No. | Volume "Day" Urine* (ml.) | Volume "Night" Urine (ml.) | Volume Ratio Night/Day Urine |
|---|---|---|---|
| 1 | 170 | 670 | 3·94 |
| 2 | 320 | 565 | 1·77 |
| 3 | 275 | 995 | 3·44 |
| 6 | 170 | 681 | 4·01 |
| 7 | 220 | 235 | 1·07 |

* Largest single volume of urine voided at hourly intervals following oral water load of 20 ml. per kg. body weight.

TABLE VI.—*Case 1. Influence of Corticotrophin and Cortisone Therapy Upon Glucose-tolerance Test*

| | Blood Sugar (mg./100 ml.) | | | | |
|---|---|---|---|---|---|
| | Fasting | ½ Hour | 1 Hour | 1½ Hours | 2 Hours |
| Before treatment .. .. | 30 | 44 | 111 | 64 | — |
| After 2 weeks' corticotrophin therapy .. .. | 90 | 60 | 90 | 95 | 95 |
| After 4 months' cortisone therapy .. .. .. | 80 | 96 | 90 | 68 | 60 |

TABLE VII.—*Case 4. Influence of Corticotrophin Therapy and of a Gluten-free Diet Upon the Glucose-tolerance Test*

| | Blood Sugar (mg./100 ml.) | | | | | |
|---|---|---|---|---|---|---|
| | Fasting | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | 2½ Hours |
| Before treatment | 80 | 80 | 65 | 80 | 80 | 80 |
| After 3 days' corticotrophin therapy | 80 | 80 | 100 | 100 | 110 | — |
| After gluten-free diet for 6 months | 100 | — | 95 | 100 | 100 | 100 |

Each patient in this series had features of deficient pituitary activity in varied degree. Adrenocortical insufficiency was universal, but increased urinary steroid excretion levels after corticotrophin administration indicated that the primary deficiency was pituitary in origin. That other adenohypophysial hormones were also involved was suggested by clinical evidence, though isotope studies in Case 1 indicated hypothyroidism and inferred thyrotrophic hormone deficiency. Normal serum electrolyte concentrations were to be expected since serum electrolyte levels are usually unaffected in anterior hypopituitarism, owing possibly to continued basal ne aldosterone secretion independent of pituitary activity (Thorn *et al.*, 1957).

## Implications of Anterior Pituitary Deficiency

### Effects of Steroid Therapy

The existence of a state of adrenocortical deficiency in intestinal malabsorption would rationalize the beneficial effects of steroid drugs in patients with childhood and adult coeliac disease (Almy, 1951; Taylor *et al.*, 1952; Adlersberg *et al.*, 1953; Finlay and Wightman, 1956; Lepore, 1958). In these disorders cortisone therapy improves absorption of fat, increases appetite and weight, and arrests diarrhoea and abdominal distension. It improves the absorption curves of glucose, vitamin A, iron, and vitamin $B_{12}$, and also the capacity to excrete an oral water-load (Kelley *et al.*, 1955; Drenick *et al.*, 1955; Glass, 1956; Nabarro *et al.*, 1957); decreased serum calcium, protein, and prothrombin levels are corrected, anaemia improves, and radiologically the intestinal deficiency pattern disappears.

Hitherto these widespread effects of adrenal steroids have been attributed to a pharmacological action, particularly their ability to suppress inflammation and thereby reduce the mucosal damage described by Paulley (1954) and since substantiated by others (Shiner, 1956; Doniach and Shiner, 1957; Sakula and Shiner, 1957; Himes and Adlersberg, 1958). According to the results obtained in the present series, many of the beneficial effects of cortisone treatment could be attributed to correction of a steroid deficiency. Such replacement therapy is supported by the effectiveness of small (physiological) doses of corticosteroids for periods up to seven years, with relapse occurring within a few weeks of withdrawing treatment (Lepore, 1958).

The effects of steroid therapy were investigated in one patient (Case 1) who had evidence of decreased adrenocortical and thyroid activity, the consequence of anterior pituitary deficiency. Her serum protein and potassium levels were normal, and she had no evidence of renal, cardiac, or hepatic disease. Steroid therapy was given in hospital over a period of five months (intramuscular corticotrophin for one month, oral cortisone four months). After her discharge she failed to attend as an out-patient until four years later, when, all treatment having ceased during the interval, she was readmitted with a less severe recurrence of her original symptoms. Re-estimation of her urinary ketosteroid excretion before and after corticotrophin administration again revealed a state of secondary adrenocortical deficiency (Table II).

During her first admission cortisone treatment was associated with a steady improvement in her mental and physical state. Her attitude altered from reluctant

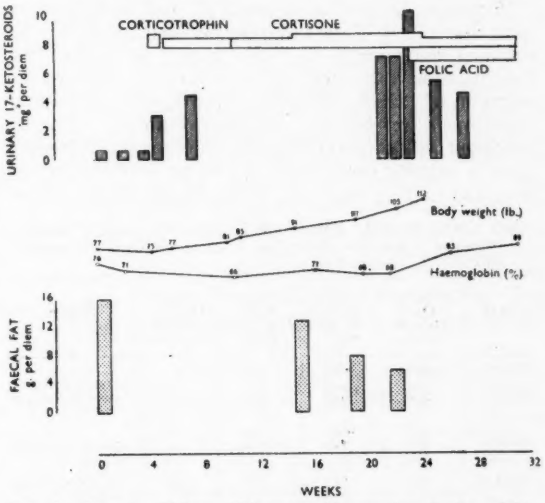


FIG. 1.—Case 1. 24-hour 17-ketosteroid excretion, body weight, haemoglobin, and faecal fat estimations, and their response to corticotrophin administration and cortisone therapy.

acquiescence to co-operation, mild depression was replaced by cheerfulness, appetite was increased, abdominal discomfort disappeared, and she gained 37 lb. (16.8 kg.) in weight in five months. While she was on a standard fat diet her average 24-hour excretion of faecal fat steadily decreased from its original level of 16 g. to 6 g. after 22 weeks' treatment (Fig. 1).

### Relationship to Abnormal Water Metabolism

Two separate mechanisms have been implicated in the phenomenon of retarded water excretion in patients with steatorrhoea: (*a*) delayed absorption of water from the intestine (Reitemeier *et al.*, 1956; Higgins *et al.*, 1957), and (*b*) impaired renal excretion (Misk *et al.*,

1958), the latter mechanism being regarded as the more important by Misk and his colleagues. A similar impairment of water excretion is seen in patients with such diverse conditions as Addison's disease, cardiac, renal, or hepatic disease, and in those with malnutrition.

That abnormal water metabolism in these varied disorders may be due to a common mechanism is suggested by the work of Mickerson and Swale (1959), who demonstrated a state of anterior pituitary deficiency with secondary adrenocortical inactivity in patients with chronic cardiac failure. It was their opinion that adrenocortical deficiency associated with continued posterior pituitary activity had induced water retention in their patients, the normal antagonism between adrenocortical and antidiuretic hormones at the renal tubule (Talbot *et al.*, 1952) failing to occur. Since a similar deficiency of anterior pituitary function has been demonstrated in patients with malnutrition (Sydenham, 1946; Jacobs, 1948; Thorn *et al.*, 1950) and in those with steatorrhoea in this and other series (Hubble, 1952; Perloff *et al.*, 1954; Bloom, 1955; Krosnick and Kalser, 1956), a corresponding pituitary-adrenal mechanism might also contribute to impaired water excretion in these disorders. This hypothesis would similarly apply in Addison's disease, in which *primary* adrenocortical deficiency would permit unopposed antidiuretic hormone activity. In each of these varied conditions steroid replacement therapy, by countering antidiuretic activity, should encourage diuresis.

Variations in diuretic response to oral water-loading were assessed in Case 1 during her first admission by equating the volume of "day urine" to that of the "night urine" to obtain a volume ratio, decrease or increase of which reflected improvement or further impairment, respectively, in water diuresis. During treatment with corticotrophin the volume ratio decreased from a pretreatment value of 3.94 to 3.53 after three days and to 2.92 after two weeks (Table VIII). After seven and nine weeks of cortisone therapy (75 mg. daily) the respective ratios were 1.62 and 1.64, but later the ratio increased to 3.13 during an attack of bronchitis. One month after recovery and with reduced cortisone dosage (50 mg. daily) the ratio was 1.75.

TABLE VIII.—*Case 1. Effects of Corticotrophin and Cortisone Therapy Upon the Ability to Excrete an Oral Water-load (20 ml./kg. Body Weight)*

| Date | Volume "Day" Urine* (ml.) | Volume "Night" Urine (ml.) | Volume Ratio Night/Day Urine | Urinary 17-Keto-steroids (mg./diem) | Therapy |
|---|---|---|---|---|---|
| 17/6/55 | 170 | 670 | 3·94 | <1 | |
| 26/6/55 | 275 | 1,070 | 3·53 | 3·2 | Intramuscular corticotrophin 60 units b.d. |
| 9/7/55 | 250 | 730 | 2·92 | 4·6 | |
| 1/9/55 | 395 | 640 | 1·62 | — | |
| 16/9/55 | 450 | 740 | 1·64 | — | Cortisone 75 mg. daily |
| 6/10/55† | 230 | 720 | 3·13 | 7·3 | |
| 21/11/55 | 380 | 663 | 1·75 | 4·7 | Cortisone 50 mg. daily |

* Volume of largest single hourly specimen following oral water-load.
† During severe bronchitis.

Though cortisone (and adrenal stimulation also) improved diuresis in this patient it did not restore a *normal* diuretic response to water-loading. This failure might be explained by an inability to correct impaired water absorption, the greater part of the improved water diuresis resulting from correction of its delayed renal excretion. In support of this view Reitemeier *et al.* (1956), using isotope tracers, were unable to increase the rate of intestinal water absorption in patients with steatorrhoea by cortisone administration. It is likely that intestinal mucosal damage accompanying steatorrhoea of long duration is permanent and incapable of being reversed by steroid therapy.

When this patient was readmitted four years later an attempt was made to estimate which of the two mechanisms, intestinal or renal, exerted the greater influence in delaying water excretion.

The diuretic response following oral and intravenous water-loading was determined before and during prednisolone therapy (15 mg. daily). Intravenous loading was assessed by substituting an intravenous infusion of 5% dextrose solution (15 ml./kg. body weight) for the oral water-load. Of the fluid administered orally only 33% was excreted within four hours, but 103% of the intravenous load was excreted over a similar period. During steroid therapy the corresponding percentage excretions were 61 and 162 (Fig. 2).

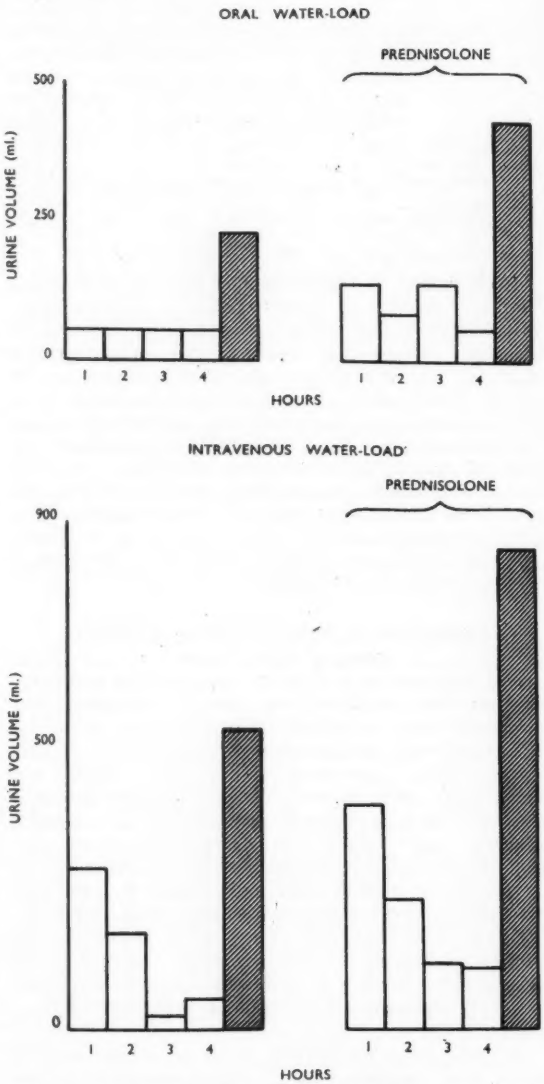


FIG. 2.—Case 1. The effects of prednisolone on the urinary excretion following oral (20 ml./kg. body weight) and intravenous (15 ml./kg. body weight) water loading.

These results indicate that, in this patient, an extra-renal (most probably impaired intestinal absorption) rather than a renal factor was mainly responsible for the delayed diuresis (see Addendum). Though the excretion of both oral and intravenous water-loads was enhanced during steroid therapy, it was not possible to determine the site of steroid activity.

#### Carbohydrate Metabolism

The association between adrenocortical deficiency and malabsorption states might also account for other metabolic abnormalities, since adrenocortical hormones are potent regulators of carbohydrate, protein, and fat metabolism. Thus could be explained low fasting blood-sugar values and flat glucose-tolerance curves in patients with steatorrhoea. The low initial fasting blood-sugar levels (30 and 57 mg./100 ml.) in Case 1 increased to normal values during steroid administration (Table VI), and in Case 4 a rise occurred in the glucose-tolerance curve after three days' treatment with corticotrophin, an improvement which was not matched by a gluten-free diet for six months (Table VII).

#### Gastric Secretory Function

The circumstances which have been postulated to explain abnormal water metabolism in patients with steatorrhoea might also explain the frequent occurrence of diminished gastric secretory activity in this disorder. That a state of adrenocortical deficiency might be incriminated is supported by the finding of depressed gastric secretion in hypopituitarism and Addison's disease and its restoration by cortisone therapy (Witts, 1958), and also by the suggestion of Kyle *et al.* (1956) that some correlation exists between gastric secretory activity and the urinary ketosteroid excretion. It is also possible that posterior pituitary activity might exert an influence, since inhibition of gastric secretion has been reported to follow pituitrin administration (Cutting *et al.*, 1937; Harries, 1956).

All five patients in this series (Cases 1, 2, 3, 5, and 6) in whom gastric secretion was investigated had an achlorhydria, and in Cases 2, 5, and 6 it was fast to histamine.

#### Blood Picture

Anaemia occurring in association with steatorrhoea may result from inadequate absorption of iron (Badenoch and Callender, 1954), folic acid (Cox *et al.*, 1958), or vitamin $B_{12}$ (Oxenhorn *et al.*, 1957; Meynell *et al.*, 1957) alone or in combination.

Five patients in this series were anaemic (Table 1); two had a normocytic anaemia, and in the remainder it was macrocytic. All five were followed until their anaemia was corrected; in each instance it responded to folic acid, vitamin $B_{12}$, or cortisone therapy; none required iron supplements.

It has been shown that patients with regional ileitis and adult coeliac disease have a reduced absorption of vitamin $B_{12}$ (Meynell *et al.*, 1957), and that this abnormality can be improved by steroid therapy. Though such inadequate absorption would account for the immediate response to intramuscular vitamin $B_{12}$ and subsequent correction of anaemia in one patient (Case 3) whose peripheral blood and sternal-marrow pictures were characteristic of pernicious anaemia, similar treatment was ineffective in two others (Cases 2 and 6) with macrocytic anaemias which later responded to cortisone administration. Clearly, improvement in these two patients could not be attributed to enhanced absorption of vitamin $B_{12}$. Furthermore, the haemopoietic effect of cortisone therapy was not dependent upon improved absorption or utilization of folic acid (Cooke, 1958), since anaemia responded to folic acid therapy after earlier failure with cortisone in Case 1, while in Case 2 cortisone was effective after folic acid had failed to maintain its initial haemopoietic stimulus.

### Discussion

The coexistence of a state of deficient adrenocortical activity found in patients with intestinal malabsorption in this series offers an explanation for certain features that are shared not only by patients with this disorder, irrespective of its cause, but also by those with Addison's disease.

It is not surprising that similar findings, previously recorded, have been attributed to malnutrition, since intestinal malabsorption is inextricably associated with a decreased calorie intake. That malnutrition should be assigned this important role is based upon a parallel with experimental animals (Gordan *et al.*, 1948; Li *et al.*, 1949; Samuels, 1950; D'Angelo, 1951) and human subjects, most of whom have been prisoners of war receiving grossly inadequate diets (McCullagh and Tupper, 1940; Sydenham, 1946; Jacobs, 1948; Thorn *et al.*, 1950). Under such circumstances "malnutrition" would imply impaired absorption to the extent of starvation, a conception which is difficult to accept in patients with steatorrhoea, however severe, since their intestinal absorption considerably exceeds that of subjects living under famine conditions. In this series decreased adenohypophysial activity could not be attributed to such dietary impoverishment. The body weight was greatly reduced in two patients (Cases 1 and 4), but one (Case 4) had the appearance of well-nourished underdevelopment rather than starvation; in every respect save that of mental ability, which was in keeping with her real age of 16, her development corresponded with that of a girl aged 9. A deficiency of dietary calories alone could not be incriminated in the remaining patients, one of whom (Case 2) was actually obese.

It is possible, however, that a qualitative dietary deficiency contributed to the development of anterior pituitary insufficiency. By virtue of its control over peripheral endocrine activity the pituitary maintains a nice equilibrium between anabolism and katabolism. Foremost in the conservation and replenishment of essential nutritional factors, the adrenocortical hormones, secreted in response to pituitary stimulation, exert considerable anabolic activity, and are potent regulators of carbohydrate, fat, protein, and electrolyte metabolism. Thus would the pituitary-adrenal mechanism be activated whenever minor deficiencies of these essential factors occur—a likely possibility with any gastro-intestinal lesion of sufficient severity to impair absorption. The longer the duration and more severe the intestinal lesion the greater will be the demand for adrenocorticoids.

Should the limit of pituitary responsiveness be surpassed by excessive or prolonged demands, anterior pituitary exhaustion will occur. In this manner the pituitary, having unsuccessfully attempted to correct the vital deficiency, allows peripheral endocrine activity to decrease, thereby reducing metabolism to a level

commensurate with nutritional supplies. Pituitary exhaustion would occur more readily when adrenocortical demands are extended by other coexistent factors—for example, infection, allergy, or hot climates (Conn *et al.*, 1948). The importance of superadded infection is well illustrated in Case 1, where the ability to excrete an oral water-load steadily improved during treatment with cortisone until respiratory infection created a demand for adrenocorticoids. The temporary deterioration in diuretic response (Table VIII) was attributed to deviation of administered steroids to the site of infection, and reduced activity at the renal tubule in consequence.

As a corollary of this hypothesis, anterior pituitary insufficiency, by inducing a state of decreased peripheral endocrine activity, particularly adrenocortical, would no longer resist the loss of essential nutritional factors via the intestine (indeed, they would not be required under such circumstances). A vicious circle would be established, with excessive loss of nutrient material in turn favouring continuation of the state of pituitary exhaustion. This circle would not be broken while the cause of pituitary exhaustion persisted, but continued steroid therapy would produce improvement by correcting adrenocortical deficiency and restoring opposition to the intestinal drain on nutrition.

Many patients with steatorrhoea may not seek advice until the state of pituitary exhaustion supervenes, by which time most of their symptoms would be due to pituitary-adrenal insufficiency *per se* or aggravation of their intestinal symptoms by such insufficiency, rather than to the primary intestinal lesion. At an earlier stage, during pituitary-adrenal stimulation, steatorrhoea may be symptomless and be discovered during routine investigation—for example, for unexplained macrocytic anaemia. During this phase symptoms and signs of corticoid deficiency would depend upon the residue of steroids available for vital activities elsewhere after a variable proportion has been utilized in attempting to correct defective absorption.

This hypothesis reinforces the statement by Cooke (1958), who emphasized that in patients with steatorrhoea the actual absorptive functions of the intestinal cell are relatively minor compared with the major metabolic functions that it performs.

## Summary

Clinical and biochemical evidence is presented to indicate a state of anterior pituitary deficiency in seven patients with intestinal malabsorption.

A possible relationship is discussed between this state of decreased adenohypophysial activity and abnormal water and carbohydrate metabolism and also gastric secretory function in patients with steatorrhoea. This state is invoked to explain a number of features which are shared by patients with intestinal malabsorption, irrespective of the causal lesion, and which occur also in those with Addison's disease. The beneficial effects of steroid drugs in steatorrhoea are attributed to correction of the secondary adrenocortical deficiency by substitution therapy.

ADDENDUM.—Since this paper was completed an intestinal biopsy has been done on Case 1 by Dr. R. A. Parkins. Extensive mucosal atrophy was present.

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In their *Report for 1958–9*, the committee of the Museum of the History of Science in Oxford record the following gifts: a scarificator for vaccination, by "Weiss, London," nineteenth century, which belonged to Dr. Paulin Martin, Clock House, Abingdon; sterilized silk sutures, sealed in glass tubes, some with the label of S. Maw, Son and Sons, London, in two metal containers, *c.* 1914; and a pocket case of surgical instruments, which belonged to Dr. Henry Watson, nineteenth century. (*Oxford University Gazette*, January 5, 1960.)

# HUMAN HYPERLIPAEMIA AND HYPERCHOLESTEROLAEMIA

## RAPID CORRECTION WITH A SULPHATED POLYMANNURONIDE*

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The "clearing" action of heparin on alimentary lipaemia (Hahn, 1943) and the associated degradation of large lipoprotein molecules (Graham *et al.*, 1951) were established some time ago and are now attributed to the activation or release of a tissue lipolytic enzyme, the so-called "lipoprotein lipase" (Korn, 1958). The further demonstration that heparin can diminish exogenous or endogenous hypercholesterolaemia in animals (Constantinides *et al.*, 1953; Friedman and Byers, 1953) and that it will decrease the development of atherosclerosis in rabbits fed cholesterol (Constantinides *et al.*, 1953; Horlick and Duff, 1954) enhanced the rationale for the clinical use of this principle in various types of blood lipid anomalies.

Unfortunately, however, heparin has been found to be only a partially effective agent in the treatment of human lipaemias. While numerous investigators have confirmed that it can decrease lactescence and produce qualitative changes in the ultracentrifugal or electrophoretic lipoprotein pattern of the serum, its action in lowering the actual concentration of any elevated serum lipid, particularly cholesterol, is inadequately documented and has been found at best to be moderate and erratic, even when it is given by continuous intravenous infusion (Basu and Stewart, 1950; Block *et al.*, 1951; Lever *et al.*, 1955).

It therefore seemed desirable to search for a more potent antilipaemic agent than heparin, and, since this substance belongs to the chemical group of sulphated polysaccharides, a large series of such compounds were synthesized and screened for antilipaemic activity (Constantinides *et al.*, 1954). Of the numerous sulphated polysaccharides screened in that study, several proved to have antilipaemic properties, in agreement with other sporadic observations (Waldron and Friedman, 1948; Brown, 1952; Glazko *et al.*, 1954; Besterman and Evans, 1957); but one class, the sulphated derivatives of seaweed (alginic) polysaccharides with a mannuronic acid repeat unit, presented the greatest interest. They displayed the most pronounced antilipaemic activity, without toxicity, in short-term rat (Constantinides *et al.*, 1954) and rabbit (Forbes and Petterson, 1953) experiments; they also proved far superior to heparin both in preventing lipaemia in acute rat experiments (Schuler *et al.*, 1957) and in attacking a hypercholesterolaemia of long standing in chronic rabbit experiments (Gutmann and Constantinides, 1955; Constantinides *et al.*, 1956; Constantinides and Saunders, 1958a)—thus arresting the progress of pre-established atherosclerosis. So far as can be ascertained from animal work undertaken to date, sulphated polymannuronides attack a lipaemia both by activating the lipoprotein lipase and by stimulating the reticulo-endothelial system (Constantinides and Saunders, 1958b), whereas heparin acts only by the former mechanism.

The present study set out to discover whether sulphated polymannuronides can attack human lipaemias as effectively as animal ones. To this end, 15 selected cases of hyperlipaemia and hypercholesterolaemia were admitted to hospital, placed on a constant lipid and calorie intake, and, after a suitable control period, given intravenous or intramuscular "paritol" (a purified brand of sulphated polymannuronides) for various periods of time. Daily serum lipid values were determined during the treatment period as well as during a pre-treatment and post-treatment interval.

### Materials and Methods

#### Lipid Studies with Paritol-C, an Intravenous Preparation

Paritol-C was given twice daily, intravenously, at 5 mg./kg. per injection, for five days to 10 male patients aged 34 to 70, with a serum total lipid range of 1,000–2,400 mg./100 ml. and a serum cholesterol range of 280–600 mg./100 ml. Of these cases, six were survivors of a proved myocardial infarction, two were hypothyroid, one had a familial lipaemia, and one had an idiopathic lipaemia. The two injections were administered at 8.50 a.m. (just before breakfast), and at 4.50 p.m. (just before supper), very slowly (1 ml. of a 10% solution per minute). Serum total lipids, turbidity, total cholesterol, and—in eight cases—phospholipids were determined every morning in blood samples obtained at 8.40 a.m.—that is, before breakfast and just prior to the morning injection. In addition, serum turbidity was determined every afternoon in postprandial blood obtained at 4.50 p.m. Case 5 constituted an exception, since prior to the usual treatment he received three injections of 1.5, 3, and 4.5 mg./kg., respectively, as well as 10 mg./kg./day (as a single injection) on three successive days.

Serum total lipids were estimated gravimetrically with a modified Bloor (1939) technique (employing acetone-ethanol as the primary extracting solvent), turbidity as previously (Constantinides *et al.*, 1956), and cholesterol by the method of Sperry and Webb (1950). Phospholipids were calculated from the lipid phosphorus values obtained after Youngburg and Youngburg (1930).

Total calorie intake and total lipid intake were kept constant from day to day and from meal to meal, throughout the entire investigation (treatment as well as pre- and post-treatment control periods). Daily total calorie intake was fixed at slightly above basal from height–age tables, while daily total lipid intake was fixed at 0.76 g./kg./day. The composition of the ingested fat was that of the average North American diet, care being taken to maintain approximately the same proportion of saturated to unsaturated triglycerides throughout the investigation. The duration of the pre-treatment control period was five days, while that of the post-treatment control interval was usually longer.

#### Lipid Studies with Paritol-M, an Intramuscular Preparation

Paritol-M was given to five male patients (Cases 11–15) aged 44 to 68 at daily dosages varying from

*This study was presented, in part, at the annual meeting of the Canadian Society for Clinical Investigation at Vancouver, B.C., on January 22, 1959.

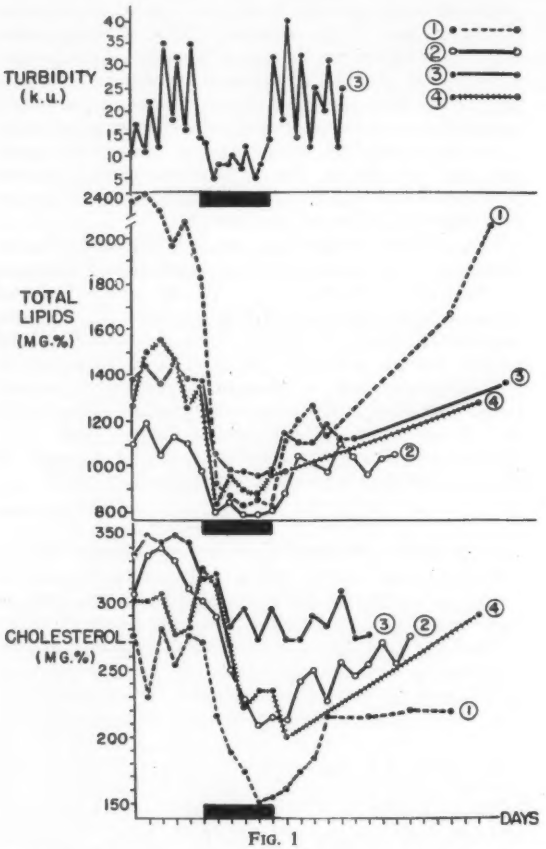


FIG. 1

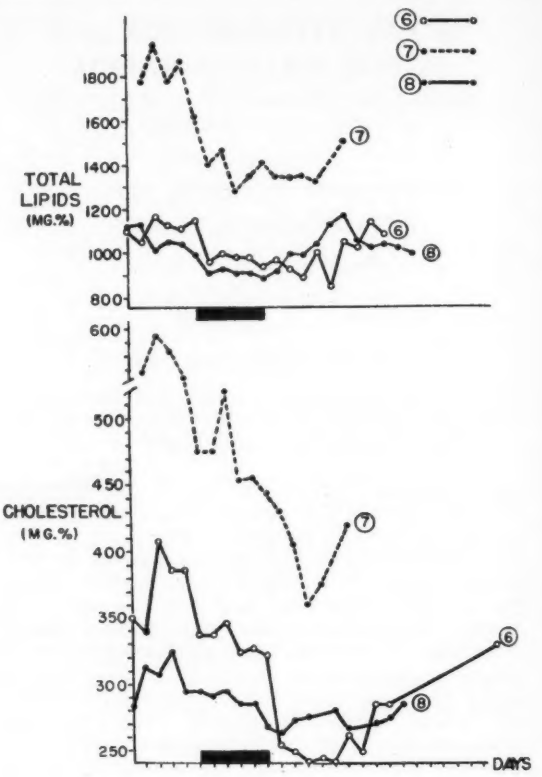


FIG. 3

1.25 to 10 mg./kg. and for periods varying from 6 to 22 days, with the purpose of determining its minimum effective dosage and its efficacy on more prolonged administration. The range of serum total lipids in this series was 1,100–1,600 mg./100 ml., that of serum cholesterol 270–430 mg./100 ml. Of these cases, two were survivors of a myocardial infarction with recurrent angina, two had manifestations of peripheral atherosclerosis (carotid artery syndrome and beginning gangrene of the toes, respectively), and one had an idiopathic lipaemia. Their general management was as in the preceding (intravenous) series, with the following exceptions: (*a*) only serum total lipids and cholesterol were determined, in fasting morning blood

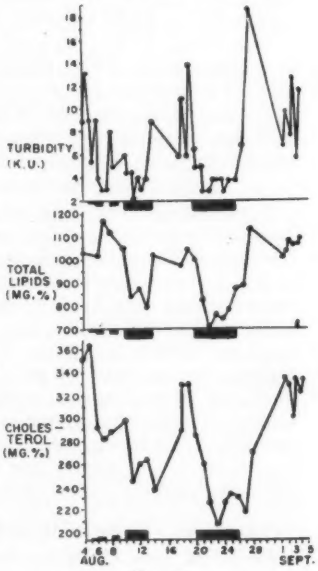


FIG. 2

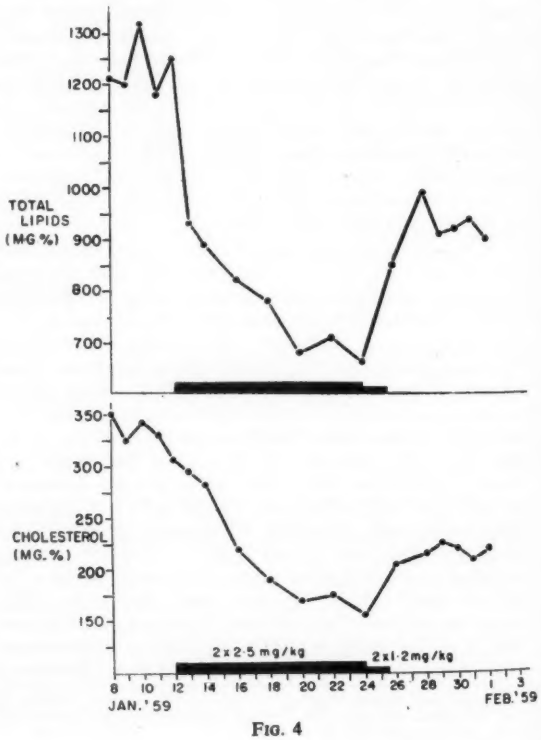


FIG. 4

samples, (*b*) total lipid intake was fixed at 1.2 g./kg./day. For comparison, two of these cases were also given intramuscular injections of heparin (Connaught's), at 1.25–2.5 mg./kg./day, for 6 to 10 days (before and after the paritol period, respectively).

#### Non-lipid Studies

To assess the general systemic effects of paritol apart from its antilipaemic action, the following studies were made in most cases, before, during, and after treatment: (*a*) *Blood:* Haemoglobin, differential count, erythrocyte sedimentation rate, serum proteins (total, albumin, globulin), clotting and prothrombin time before and 1, 6, and 24 hours after drug injection. (*b*) *Liver-function tests:* Serum bilirubin (direct and indirect), alkaline phosphatase, thymol turbidity, cephalin-cholesterol flocculation, bromsulphalein excretion at 30 minutes. (*c*) *Kidney:* serum non-protein nitrogen, complete urinalysis. (*d*) *E.C.G.* Daily body weight, blood-pressure, pulse, and temperature were recorded throughout every patient's stay in hospital.

## Results

#### The 10 Cases Given Intravenous Paritol-C

Figs. 1–3 give details of this group of cases. To save space, data from only the first eight are presented graphically: Cases 1–4 are grouped together in Fig. 1 and Cases 6–8 in Fig. 3. Furthermore, since the serum turbidity response to treatment was identical in almost all cases, only two turbidity figures are presented—those of Cases 3 (Fig. 1) and 5 (Fig. 2)—to serve as examples of all the others.

It can be seen at a glance that in all of these cases there was marked response to treatment by one or more criteria, the elevated serum lipids dropping rapidly towards normal values during the injection period and returning partially or completely to their previous high levels upon withdrawal of the drug. An exception to this general pattern was seen in Cases 6 and 7 (the two hypothyroid patients), whose serum cholesterol response to treatment was somewhat delayed when compared with the others.

If it is considered that serum with turbidity values greater than approximately 15 was visibly milky, a study of Case 3 (Fig. 1) shows that in the pre-treatment period the turbidity was swinging daily, the serum being least turbid every morning, after the night's fast, and becoming most turbid every afternoon, postprandially.

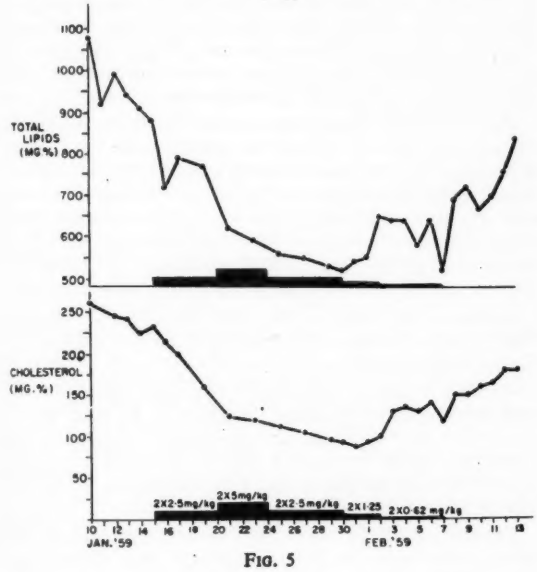


FIG. 5

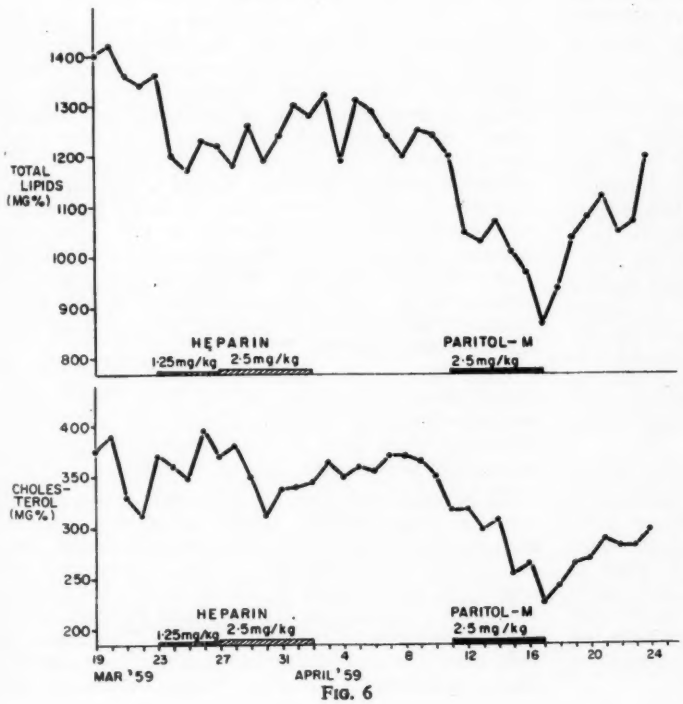


FIG. 6

### LEGENDS

FIGS. 1 (Cases 1–4), 2 (Case 5), and 3 (Cases 6–8).—The black boxes indicate the intravenous paritol-C treatment periods. With the exception of Case 5, all others received I.V. 5 mg./kg. of this drug twice daily for five days. Case 5 received in succession three single daily injections of 1.5, 3, and 4.5 mg./kg., respectively, then 10 mg./kg. once daily for three consecutive days, and finally 5 mg./kg. twice daily for six days. Serum turbidity is expressed in Klett units (K.U.)—that is, direct readings of the Klett–Summerson colorimeter, while serum total lipids and serum cholesterol are expressed as mg. per 100 ml. of serum. All values are plotted synchronously.

FIGS. 4–6 (Cases 11, 12, and 15 respectively).—The black boxes indicate the intramuscular paritol-M treatment periods, while the shaded boxes in Fig. 6 indicate the intramuscular heparin treatment interval. Dosages of drugs varied as recorded in the graphs. Serum total lipids and cholesterol are expressed and plotted as in the preceding intravenous series.

Paritol treatment promptly suppressed both the fasting and the postprandial lactescence, keeping the serum clear all day throughout its administration, this effect being reversed immediately upon withdrawal of the drug. The marked depression of serum turbidity values during treatment, exactly as illustrated in Cases 3 and 5 (Figs. 1 and 2), was obtained in all except Case 10—in which the serum was continuously clear even before treatment was started.

If it is further considered that the upper "normal" limit of serum total lipids is 800–900 mg./100 ml. and that of serum cholesterol 240 mg./100 ml., it can be seen that this treatment caused a return of the total lipids to normal values within 24 hours in seven cases (Nos. 1–6 and 8); it caused a return of the cholesterol to normal within 48 hours in four cases (Nos. 1, 2, 4, and 5) and depressed it significantly within six days in another four cases (Nos. 3 and 6–8).

Cases 9 and 10 were those with only partial or minimal response to treatment. Case 9 showed a marked turbidity response but no significant depression of total lipid or cholesterol values, which were close to normal, however, before treatment began. Case 10 displayed only a slight and transitory total lipid depression and deserves special attention, since, in addition to his hyperlipaemia, this patient also had tuberous xanthomatosis and was suffering from rheumatoid arthritis, requiring continuous glucocorticoid treatment (5 mg. of prednisone t.i.d.). Thus in this case paritol was given in the presence of steroid treatment.

In the eight cases in which they were studied (Nos. 1–6, 8, and 10) the serum phospholipids were found to parallel closely the changes of serum cholesterol levels. Thus, in all except Case 10, paritol caused a significant reduction of the serum phospholipid value, with a slow return towards the previous level after withdrawal of the drug. Since, however, the cholesterol was reduced more than the phospholipid, the cholesterol: phospholipid ratio decreased significantly in most instances during treatment.

### The 5 Cases Given Intramuscular Paritol-M

The intramuscular preparation of paritol had a prompt and pronounced antilipaemic effect in all five cases, with a sustained action over the more prolonged periods during which it was tested (up to three weeks). In view of this uniform response, data from only three of the five cases are presented graphically (Figs. 4–6).

Dosage studies in Cases 12 and 13 indicated that the minimum effective dosage with regard to serum cholesterol depression was approximately 2.5 mg./kg. once daily. Even smaller amounts, however, seem to affect serum total lipids and turbidity, as shown by untabulated data. The full cholesterol-depressing effect took up to 72–96 hours for its manifestation, at the dosages tested.

In the last two cases the minimum effective dosage of paritol was compared with equivalent amounts of heparin, administered in identical fashion and given either before (Case 15) or after (Case 14) the polymannuronide. As can be seen in Fig. 6, given at 2.5 mg./kg./day for six days, paritol-M significantly depressed both serum total lipid and cholesterol levels, whereas heparin failed to influence either of these two serum constituents. Similar results were obtained in Case 14.

### Non-lipid Studies in All Cases

*Blood.*—At all dosages and routes given, paritol did not alter the blood haemoglobin, cell numbers, or morphology, and it did not affect the erythrocyte sedimentation rate or the serum proteins. A single intravenous dose of 5 mg./kg. was moderately anticoagulant, prolonging the Lee–White clotting-time to 20–40 minutes one hour after injection, with a return to normal five hours later. This dosage level usually also depressed the prothrombin time to 70–80% of normal one hour after injection, with a return to normal within six hours, except in the two hypothyroid patients in whom the depression was greater and lasted longer. Given at 3.5 mg./kg. intramuscularly or less, however, the drug had no effect on the Lee–White clotting-time or prothrombin time. There was no effect on the bleeding-time under any circumstances.

*Liver.*—Paritol did not alter hepatic function as judged by any of the six criteria employed. In two cases, however, that were admitted with a moderately depressed hepatic function before treatment was started (Cases 6 and 11) a further slight rise of the 30-minute bromsulphalein retention (from 14% to 31% and from 12% to 27%, respectively), without a change in any other hepatic parameter, occurred during the injection period.

*Kidney.*—As judged by the consistently normal N.P.N. and urinalysis, the treatment did not alter renal function in any case.

*General Clinical Findings.*—Blood-pressure, pulse, and temperature remained unaffected by the drug. There was no significant change of body weight during treatment, except in Cases 5 and 12, in which there was a slight loss of weight (2 and 1 kg., respectively) during the period of high-dosage injection.

Despite occasional side-effects in half the cases of the intravenous series at the high-dosage level (5 mg./kg. twice daily), the drug was on the whole well tolerated, and almost all patients expressed the desire to continue this treatment after discharge. Side-effects at the high intravenous dosage consisted of transitory paraesthesiae (Cases 1–5) ranging from "tingling" or "pressure" sensations in tongue, scalp, or extremities to "muscle pains"; these appeared from one-half to one hour after injection (usually only in the initial treatment period), and lasted for a few minutes. Patient 5, who for three days received the highest amount of paritol ever given in a single intravenous injection in this study (10 mg./kg.), claimed that he experienced a fainting spell after three such injections. A slight loss of scalp hair occurred in the same patient at about a month after treatment, lasting for a few weeks, but it was rapidly and completely restored.

There were no side-effects of any sort at the lower-dosage levels 2.5 mg./kg./day or less). The intramuscular injections occasionally produced slight local discomfort when given in high concentration or large volume, but small doses caused no complaints.

All patients who were admitted with symptoms of vascular origin claimed marked relief or complete disappearance of these symptoms during treatment and for several weeks thereafter. This was claimed of angina pectoris (Cases 2, 3, 5, 6, 8, 9, 10, 14, and 15), intermittent claudication (Cases 5 and 9), pain from incipient gangrene of the right great toe (Case 12), and right-sided recurrent paresis and numbness in a carotid artery syndrome (Case 13). During treatment the

nitroglycerin requirements of most angina cases greatly decreased or disappeared, local circulation visibly improved in the afflicted toes of patient 12 (as judged by colour, temperature, and dorsalis pedis pulsation), and there was marked acceleration in the slow cerebration of the patient with the carotid syndrome. It should be pointed out, however, that as the paritol injections were not controlled by placebo injections the above improvements in symptoms of vascular origin may have been entirely subjective.

## Discussion

The above results show that paritol caused a very rapid return to normal or a marked reduction of the elevated serum total lipid and cholesterol values in the majority of the hyperlipaemic patients to whom it was given. The antilipaemic effect was obtained with the intramuscular as well as with the intravenous route of administration, it was sustained for the duration of the treatment, and it was reversed only gradually after withdrawal of the drug. In the most responsive cases the dramatic action of this principle on hyperlipaemia was comparable to the effect of insulin on hyperglycaemia. Indeed, in one instance high amounts of the drug depressed the serum cholesterol value below the generally accepted lower limit of normal (cf. Case 12).

Compared with heparin, milligram for milligram, paritol proved by far the superior agent for reducing cholesterol and total lipid values, thus confirming in the human the results of animal experiments under both acute (Schuler *et al.*, 1957) and chronic conditions (Constantinides *et al.*, 1956). The effectiveness of paritol will be further appreciated if it is considered that it successfully cleared the serum turbidity of the persons with coronary disease, a group whose serum lactescence has been reported to be refractory to the clearing action of heparin (Block *et al.*, 1951).

At higher dosages (5 mg./kg. or more), paritol exhibited its known moderate anticoagulant action and occasional side-effects (Sollmann, 1957), but at lower dosages (3.5 mg./kg. or less) it showed neither anticoagulant action nor side-effects, while maintaining its full antilipaemic activity—in agreement with findings in animals (Constantinides and Saunders, 1958b). Since alopecia and other side-effects are encountered only with high anticoagulant dosages of sulphated polysaccharides (including heparin) (Fischer *et al.*, 1953; Sollmann, 1957), it can be anticipated that low subanticoagulant dosages of paritol would permit effective long-term control of hypercholesterolaemia without any undesirable manifestation. Repository preparations requiring only one or two intramuscular injections a week would seem the ideal method of administration for chronic treatment.

The precise mechanism through which sulphated polymannuronides depress cholesterol level in the blood is not yet known. Though they have been shown to activate the lipoprotein lipase (Constantinides *et al.*, 1954) and to stimulate removal of lipids by the reticulo-endothelial system (Constantinides and Saunders, 1958b), a detailed fat balance study is needed in order to determine the fate of the lipids they drive out of the blood-stream. From the data obtained so far it appears that—at least with the intravenous route of administration—the serum concentration of triglycerides decreases first, followed after a slight time-lag by the drop in cholesterol concentration.

The great majority of positive results were obtained in the absence of any detectable change of hepatic function or body weight. In the two cases where the pre-existing hepatic dysfunction was somewhat aggravated by the high-dosage treatment, as well as in the two cases that showed a slight loss of body weight under the same circumstances, there was no correlation whatsoever between these phenomena and the lipid movements. Thus, serum lipid depression in these cases occurred only *after* hepatic function improved or well *before* loss of body weight was manifested, respectively.

It is of interest that the only refractory case of this study was maintained on glucocorticoids before and during the paritol treatment. Since it has been found in animals that glucocorticoid-supported lipaemias are resistant to the clearing action of heparin (Constantinides *et al.*, 1955), the concurrent steroid treatment may have been responsible for the refractory nature of that case. On the other hand, as this case also presented tuberous xanthomata, it may well be that some or all hypercholesterolaemias associated with xanthomatosis are resistant to the action of sulphated polymannuronides, possibly because of an unresponsive reticulo-endothelial system. More work is needed to clarify this problem.

Though the marked subjective improvements claimed by most patients should not be overlooked, they cannot be assessed critically in the present study, which was not designed for that purpose. A placebo-controlled investigation, using the "double blind" technique and objective end-points, will be necessary before any conclusions on vascular effects can be drawn.

In overall appraisal, paritol offers great promise as a treatment for lipaemias which are resistant to heparin or other agents and for cases where an immediate reduction of blood lipids is required. Further research is indicated on its precise mechanism of action and on the most responsive types of lipaemias.

## Summary

Paritol, a synthetic sulphated polysaccharide with a mannuronic acid building block, was given under conditions of controlled calorie and lipid intake to 15 hospital cases of hyperlipaemia and hypercholesterolaemia for periods ranging from five days to three weeks. Serum total lipids, cholesterol, turbidity, and in most cases phospholipids were determined daily throughout the treatment period as well as during pre-treatment and post-treatment control intervals.

This principle proved capable of exceedingly rapid and intense action on the elevated serum lipids, both intravenously and intramuscularly. It caused a return to normal of the total lipid values within 24 hours and of the cholesterol values within 72 hours in 10 cases, while reducing them greatly within a slightly longer interval in another four cases. The antilipaemic effect was sustained for the duration of the treatment, and it was gradually reversed after withdrawal of the drug.

The minimum effective cholesterol-depressing dose by the intramuscular route was found to be 2.5 mg./kg./day. At this dosage paritol showed no anticoagulant action or side-effects, and it displayed a far greater antilipaemic activity than equivalent amounts of the natural sulphated polysaccharide heparin.

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"The triennial reports of the [joint Bethlem Royal Hospital and Maudsley] hospital have two objects. The first is the provision of statistics relating to the medical administration of the hospital departments. The second is the provision of demographic, social, and diagnostic data on the patient population attending the hospital. While these two objects have much in common, there is a basic difference between them. The administrator is concerned with the amount of work done by the various departments of the hospital in providing treatment for its patients. This work is most conveniently assessed by taking into account the total number of admissions of patients to (or their discharges from) a department during a given time. On the other hand, statistics relating to demography, social factors, and diagnoses need for the most part to be based on the number of individual patients that attend the hospital, irrespective of the number of occasions on which they are admitted. As compared with previous reports, the present report puts rather more emphasis on the clinical and rather less on the administrative aspects of the data. One of the principal objects of this change is to allow the presentation of data concerning the whole population attending the hospital. Most of the published data on the statistics of mental illness in Great Britain deal only with in-patients. But psychiatric hospitals are becoming increasingly concerned with out-patient care and treatment. Moreover, because of changes in administration and in treatment, many cases that a few years ago would have been treated as in-patients are now treated as out-patients. There is consequently an increasing need for clinical statistics on all patients under care at psychiatric hospitals and not merely on the in-patients. It is in the belief that hospital statistics of this kind will have a growing value that the present editor has emphasized the clinical aspects of the data." (*Triennial Statistical Report: Years 1955–7*. Bethlem Royal Hospital and the Maudsley Hospital.)

# TOTAL PARALYSIS REGIME IN SEVERE TETANUS

BY

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In an era of remarkable therapeutic advances the search for an effective treatment of severe tetanus has been disappointing. In New Orleans, Creech *et al.* (1957) demonstrated a small and steady decline in mortality over the past fifty years, but were unable to relate this fall to the many changes in treatment. In Malaya tetanus is common: from 1952 to 1956 an average of 20 patients with tetanus (excluding neonatal tetanus) have been admitted each year to the Penang General Hospital. About one-third of these victims were children. The mortality was 40%, varying yearly from 20% to 50%. We soon recognized that patients with mild tetanus recover with conservative treatment.

Our concern in this paper is confined to non-neonatal severe cases—patients who develop generalized spasms that stop respiration despite conservative treatment. In 1957 we started treating such patients with the total paralysis regime (T.P.R.), consisting of tracheostomy, total paralysis of skeletal muscles, and intermittent positive- or positive/negative-pressure artificial respiration. In reviewing our experience with this treatment, the two main questions we wish to consider are: (1) How may severe tetanus be recognized at the outset? (2) Is the T.P.R. effective in treating severe tetanus?

## Material and Methods

All patients aged over 6 with tetanus were admitted under the charge of one of us (S. M. A. A.), those aged 6 or less under the charge of D. P. B. During the 16 months June, 1957, to September, 1958, a total of 40 consecutive cases were seen (excluding neonatal tetanus) and 11 were selected for treatment with T.P.R. One subject died during tracheostomy on the day of admission and has not been included in the series. Details of age, site of infection, incubation period, onset period (the time between the first symptom and the first spasm whether local or generalized), duration of T.P.R., and result in the 10 patients are given in the Table.

All patients received antiserum (50,000 to 100,000 units), intramuscular chlorpromazine (50–100 mg. four- or six-hourly), intravenous thiopentone, and crystalline penicillin. Four patients in addition had promethazine, 25 mg. 12-hourly, and sodium amylobarbitone, 200 mg. six-hourly. If feasible, the wound causing the infection was excised at a suitable interval after starting the antiserum. When it seemed that this conservative treatment was failing, all consultants met to assess the

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*Details of Cases*

| Case No. | Age | Site of Infection | Incubation Period in Days | Period of Onset in Hours | Duration of T.P.R. in Days | Result |
|---|---|---|---|---|---|---|
| 1 | 14 | Foot | 13 | 24 | 12 | Lived |
| 2 | 31 | Uterus | 5 | — | 7 | Died |
| 3 | 11 | Foot | 4 | 24 | 11 | Lived |
| 4 | 44 | Toe | 7 | >48 | 5 | Died |
| 5 | 6 | Knee | 9 | <24 | 6 | ,, |
| 6 | 2 | Middle ear | 6 | 36 | 2 | ,, |
| 7 | 42 | Uterus | 3 | 12 | 3 | ,, |
| 8 | 6 | Middle ear | ?6 | >36 | 5 | ,, |
| 9 | 29 | Foot | 2 | 12 | 6 | ,, |
| 10 | 4 | Leg | 3 | 24 | 5 | ,, |

case. In some instances T.P.R. was instituted immediately, but in others we first tried intensifying the conservative treatment. When this also failed T.P.R. was started. In 9 of the 10 cases the chief indication for T.P.R. was one or more spasms severe enough to stop respiration despite the treatment given. In Case 2, however, T.P.R. was induced on admission in view of the known severity of post-abortion tetanus. In Case 4 T.P.R. was begun three hours after admission, in Case 7 one week after admission, and in the other seven cases within 24 to 48 hours of admission.

### General Management of T.P.R.

The general management of the respiration unit was the combined responsibility of us four consultants. Our registrars and house staff were available for duty with the unit, thus providing a doctor on immediate call throughout the period of treatment. One consultant was always on 10-minute call and was responsible for the care of the patient during his spell of duty. A medical and nursing plan was recorded, and was amended as experience suggested. The unit was located in a side-ward under the general direction of the ward sister. Additional nursing staff was posted to the ward to provide one staff-nurse and one second-year nurse with the patient throughout the 24-hour period. We managed to build up a nucleus of nursing staff familiar with the management of these cases; the majority took great pride in the special experience and responsibility which this exacting work requires. To minimize staff disturbance one of us (D. P. B.) at a later date started the nursing of children on T.P.R. in the open ward. The sister and senior staff-nurse (both with prior experience of T.P.R.) supervised junior nurses who managed the regime. The system worked well and obviated the need for additional nursing staff.

When it was decided to use T.P.R., atropine was given intravenously followed by thiopentone and suxamethonium. After oral intubation a high tracheostomy was done and a cuffed endotracheal tube suitably shortened was inserted through the tracheostome. We tried various types of tube, but prefer ordinary endotracheal tubes with a short cuff. It lies more comfortably in the neck than would at first seem likely and is not prone to kink. L-shaped tubes have not in our experience been satisfactory. Magill's suction T-piece connexions of light metal with rubber cap are suitable connectors. We experimented with many devices to secure the tracheostomy tube, but have come to the conclusion that it is best to use only a length of tape tied behind the neck and to disconnect the tube from the machine during the few seconds in which the patient is being turned over in nursing procedures. The passing of a gastric tube in an unrelaxed subject with tetanus is dangerous and may precipitate a severe general spasm, vomiting, and subsequent inhalation of vomit. We prefer to delay passing the "polythene" stomach-tube until the tracheostomy has been done.

As soon as respiration returned after the initial dose of suxamethonium, full curarization was obtained by intravenous D-tubocurarine. Thereafter paralysis was maintained by giving D-tubocurarine intramuscularly together with hyaluronidase. This was fully effective, but there was a delay of 7 to 10 minutes before maximum effect was reached. The most reliable indication for a further dose of relaxant was the faintest twitching movement of the trachea on gentle manipulation of the tracheostomy tube. A second useful sign was a flicker of diaphragmatic movement at the end of inspiration. Twitching movements of the fingers mentioned by Powell *et al.* (1958) occur later, and by the time they are evident there is usually a reduction in respiratory minute-volume due to increased resistance in the thorax. The dosage of D-tubocurarine varied from 4 to 30 mg. every one to two hours, and was remarkably constant in individual patients.

Because prolonged sedation is itself a hazard the use of narcotic drugs was kept to a minimum. In early cases sodium amylobarbitone, 0.2 g. six-hourly, was given via the gastric tube. It seems unlikely this dosage could account for the amnesia which the two survivors had for the duration of the T.P.R. Both these patients during the first few hours after stopping the T.P.R. were restless when breathing spontaneously (though the minute-volume was satisfactory), but fell promptly asleep when the machine was started again. In Cases 6, 9, and 10 all sedation was stopped once T.P.R. was started. Fluid and nutritional requirements were given every two hours via the gastric tube as a milk mixture fortified according to the patient's age and weight. During the first 24 hours of T.P.R. the amount per feed was progressively increased from (in adults) 55 to 230 ml.; thereafter the 24-hour total was 2.75 litres, supplying 2,600 calories, 75 g. of protein, 3 g. of sodium, 5 mg. of aneurine, 5 mg. of riboflavine, 125 mg. of ascorbic acid, 50 mg. of nicotinic acid, and 0.6 g. of ferrous sulphate.

Intermittent positive-pressure respiration (I.P.P.R.) was provided by a Radcliffe respirator. In Cases 1 to 5 this was of the single-phase type. Generally speaking, we did not find the flutter-valves of this machine satisfactory. For a given pressure each valve would give a different minute-volume, though valves with silicon rubber were more consistent. The "perspex" casing of the valve tended to crack after some days' handling. In the last five patients the newer Radcliffe respirator providing a negative phase and having cam-operated valves was used. This machine was much more satisfactory.

A respiratory rate appropriate to the age of the patient was chosen and the respiratory pressure was then adjusted to provide the desired minute-volume, which was usually higher than that indicated by the nomogram of Radford (1955). In patients on T.P.R. there is a continuous fluctuation in pulmonary function. Variation in the resistance of thoracic muscles with the degree of curarization, and the constant tendency for secretions to accumulate, interfere with ventilation. In our experience frequent clinical appraisal, particularly of sweating, blood-pressure, pulse, chest auscultation,

and minute volume as recorded by the machine, gave adequate indication of any failure in ventilation, etc.

Biochemical estimations were made and chest radiographs taken, but these were of no significant help in the minute-to-minute management of the patient. The nursing staff soon learnt to appreciate these clinical observations (including chest auscultation), and if matters were not righted by turning, suction, percussion, and compression of the chest, their instructions were to inform the doctor on call. Patients were turned every two hours as a routine. Tracheal and bronchial toilet, using a Tiemann catheter, was done as indicated, usually by the nursing staff, who also percussed and squeezed the chest to assist drainage. A "wet chest" is disastrous in T.P.R. (or, for that matter, in tetanus generally), and in preventing this our watchword soon became "keep the patient off his back." The semi-prone or occasional lateral positions promote drainage of secretions by gravity and prevent infection. Apart from penicillin for the tetanus infection, no antibiotics were given as a routine. When hypotension developed, individual patients were given steroids, noradrenaline, and other drugs as indicated in the case-summaries.

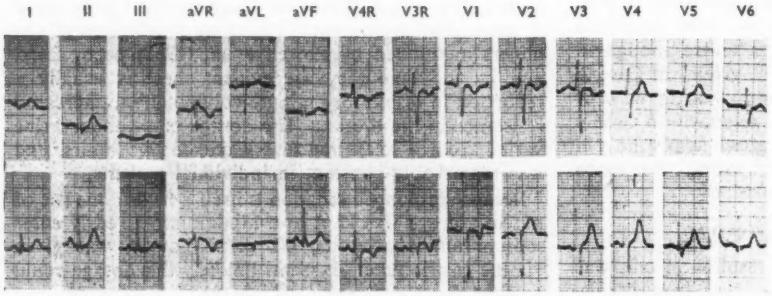


FIG. 1.—Case 1. First E.C.G., on second day of T.P.R. (top row, June 29) shows inverted T waves which become upright in V2 and V3 four days later (bottom row, July 3). The patient recovered.

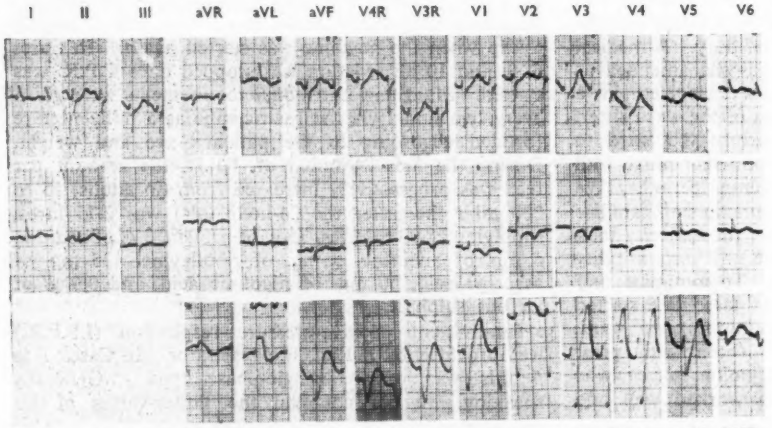


FIG. 2.—Case 2. T.P.R. was started July 12, 1957: hypotension started February 15, 1957: diastolic B.P. was raised by noradrenaline, and the first E.C.G. (top row, July 16) shows upright T waves. Two days later, when hypotension had become increasingly resistant to noradrenaline, T is inverted in right chest leads. The third E.C.G., 15 minutes before death (bottom row, July 19) shows gross conduction defect.

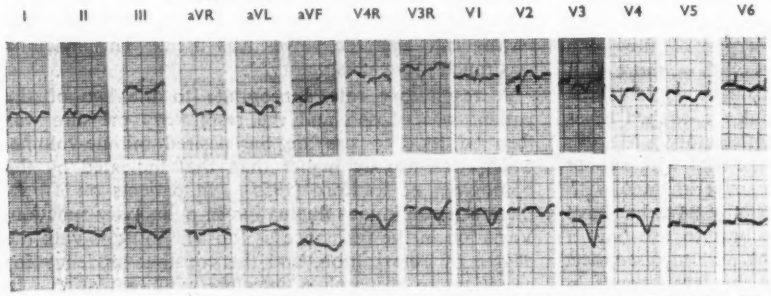


FIG. 3.—Case 5. T.P.R. was started October 12, 1957: hypotension developed October 16. E.C.G.s on October 17 (top) and 18 (bottom) show that T inversion became progressively more marked in chest leads Patient died on October 18.

## Results

Only two patients out of the 10 survived (see Table). In Case 10 we probably stopped T.P.R. prematurely, but in six cases lethal hypotension developed, usually when everything appeared to be progressing satisfactorily. Some of the salient clinical features are outlined in the case-summaries.

*Case 1.*—A Chinese boy aged 14 was admitted on June 27, 1957, with generalized spasms not interfering with respiration. Despite conservative treatment the spasms became more severe, and T.P.R. was started on June 28. A temperature of 105° F. (40.6° C.) was recorded that day, but thereafter progress was satisfactory and hypotension did not develop. However, the first electrocardiogram (E.C.G.), on June 29, showed symmetrical T inversion in leads V4R to V3. In the second record, on July 3, T was upright in V2 and V3 (see Fig. 1). The serum potassium was 5 mEq/l. and serum sodium 135 mEq/l. T.P.R. was stopped on July 10, but for the next 48 hours, after cessation of D-tubocurarine, respiration required assistance. Mild generalized spasms continued for three days but were controlled by chlorpromazine. The tracheostomy tube was removed on July 13, the tracheostome had healed by July 19, and the patient was discharged well on August 7.

*Case 2.*—An Indian woman aged 31 had a procured abortion on July 6, 1957, developed trismus on July 11, and was admitted on July 12. T.P.R. was instituted immediately, and her condition remained satisfactory until July 15, when the B.P. dropped to 60/40. A noradrenaline drip raised the diastolic B.P. to 80, but the systolic remained at 100 or less. The first E.C.G., on July 16, showed upright T waves in all chest leads. The second, on July 18, showed symmetrical T inversion in V3R to V4, maximal in V3. Meanwhile hypotension became increasingly resistant to noradrenaline despite progressively increasing the dose so that the concentration was 192 mg. in 540 ml. (at 30 drops a minute) on July 19, when she died. A third E.C.G. taken 15 minutes

before death showed wide biphasic complexes indicating gross conduction defect (see Fig. 2).

*Case 3.*—An Indian boy aged 11 was admitted on July 20, 1957, and T.P.R. was started on July 22, when conservative treatment had failed and spasms were stopping respiration. Progress was satisfactory and hypotension did not supervene. The first E.C.G., on July 25, showed symmetrical T inversion 4.5 mm. deep in V1 and biphasic T waves in V2 to V4. The second record, on July 29, showed upright T waves in V2 to V4. T inversion in V1 was only 1 mm. deep. T.P.R. was stopped on August 2, and though generalized stiffness continued there were no spasms. The tracheostomy tube was removed on August 9, the tracheostome had healed by August 12, and the patient was discharged fully recovered on August 24.

*Case 4.*—An Indian man aged 44 was admitted with generalized spasms on September 13, 1957. Initially, conservative treatment appeared successful, but later on September 13 a violent spasm stopped respiration and caused collapse of the patient. T.P.R. was therefore started, and progress was satisfactory until 2.45 p.m. on September 16, when the B.P. dropped to 80/50. Intravenous digoxin, 0.5 mg., was given, and the B.P. rose to 110/90 (noradrenaline was not given). The first E.C.G., on the morning of September 16, was taken when the B.P. was normal, and it showed a 1-mm. horizontal depression of ST segment in V5 and V6. Oral digoxin was continued, 0.25 mg. 12-hourly. Thereafter there were fluctuating irregularities in the pulse, and at 8.30 a.m. on September 18 hypotension again supervened. It was not relieved by noradrenaline, and the patient died at 5.30 p.m. A second E.C.G., at 3.30 p.m., showed a 2-mm. S-T elevation in V1 and V2 but no other significant change.

*Case 5.*—A Chinese boy aged 6 was admitted on October 12, 1957, and T.P.R. was started later that day. Hypotension developed at 5.30 p.m. on October 16 and remained resistant to noradrenaline and intramuscular cortisone, 50 mg. six-hourly, until his death at 9 p.m. on October 18. The first E.C.G., on October 17, showed symmetrical T inversion in V3 to V6. The second E.C.G., on October 18, showed further deepening of T inversion and extension to involve all chest leads (see Fig. 3).

*Case 6.*—An Indian boy aged 2 years was admitted on March 25, 1958. T.P.R. with the newer positive-negative Radcliffe respirator was started on March 26, when spasms interfering with respiration occurred despite conservative treatment. Progress appeared satisfactory until the evening of March 28, when, without obvious cause, he suddenly died. His blood-pressure was normal 45 minutes before death.

*Case 7.*—A Chinese woman aged 42 was admitted on June 9, 1958, after an abortion. Tracheostomy was performed shortly after admission, but otherwise the conservative regime was followed until June 16, when increasing spasms culminated in respiratory arrest. T.P.R. was therefore started. On June 17 the pulse was irregular, and next day hypotension supervened, continuing despite intramuscular cortisone and repeated intravenous methylamphetamine hydrochloride until the patient died on June 19. No E.C.G. records were obtained, but necropsy showed toxic myocarditis (see Fig. 4).

*Case 8.*—A Malay girl aged 6 was admitted on July 28, 1958, with trismus of uncertain duration. Spasms which started 36 hours after admission continued despite conservative treatment. The $CO_2$ combining power had dropped to 18 mEq/l. on July 30, when T.P.R. was started. On July 31 it had risen to 25 mEq/l., and thereafter remained normal. Daily serum sodium and potassium levels remained within the normal range. On August 3 there were episodic pulse irregularities, and on August 4 hypotension developed at 6.30 p.m. There was no significant improvement with noradrenaline, and the patient died at 9.30 p.m. E.C.G. records obtained on July 29 and 31 and August 1 and 3 showed a monophasic R wave in V4R and V3R. R exceeded S in V1, but there were no significant changes in serial records.

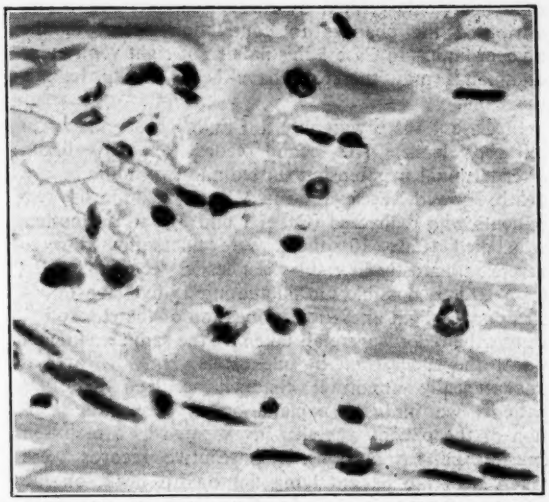

FIG. 4.—Case 7. Patient died after three days' T.P.R. and two days' hypotension. Heart showed a toxic myocarditis. Interstitial oedema and infiltration with mononuclear and occasional plasma cells. A few muscle fibres showed fragmentation, cellular reaction being minimal. (×500.)

*Case 9.*—A Malay man aged 29 was admitted on August 8, 1958, and T.P.R. was started on the 10th. Hypotension lasted from 3 to 10 a.m. on August 14, but then responded to methylamphetamine. Thereafter the pulse was irregular for brief episodes. Hypotension recurred on August 16 between 8.30 and 9 a.m. and again at 6.30 p.m., the patient dying at 7.10 p.m. E.C.G. records were taken on August 10, 14, and 16. They were normal. Unfortunately no record was obtained during a hypotensive phase. Daily serum potassium and sodium on August 10 to 16 were normal.

*Case 10.*—A Chinese boy aged 4 was admitted on September 2, 1958, but, despite intensifying the conservative regime, spasms increased and $CO_2$ combining power fell to 16.5 mEq/l. on September 3, when T.P.R. was started. On September 4 it rose to 22 mEq/l. and thereafter remained normal. Control of tetanus toxaemia was satisfactory, but amoebic and Sonne dysentery developed. The infection responded to emetine and sulphonamide. On September 8 T.P.R. was stopped. Progress appeared satisfactory, though chlorpromazine was still required to control occasional spasms. However, on September 17 bronchopneumonia was evident, and the patient died the following day. Thirteen E.C.G. records were taken between September 3 and 11. The fourth record, on September 5, and the eighth, on September 8, showed deep symmetrical T inversion in V4. In the other 11 records T was upright in this lead.

## Electrocardiography

Serial E.C.G.s were obtained during T.P.R. in all except Cases 6 and 7. Standard, unipolar, and eight chest leads (V4R to V6) were taken as a routine, but in Cases 8 and 10 leads V3R and V3 or V4 were often omitted as the chest was too small. In Case 9 the three records were normal, but the E.C.G.s were not taken when hypotension was present. In Case 8 there was a monophasic R in V4R and V3R, and R exceeded S in V1 though there were no significant changes in serial records (again no record was obtained during hypotension). Gailani *et al* (1958) found similar E.C.G. changes in patients with muscular dystrophy. They excluded pulmonary hypertension and

right heart enlargement by cardiac catheterization and attributed the changes to conduction defect in the myocardium. In Case 8 this pattern of right ventricular dominance may therefore have been due to tetanus toxaemia.

In Case 4 there was only a 1-mm. ST depression in left chest leads. The second record, taken five hours after terminal hypotension started and two hours before death, showed ST elevation in V1 and V2. In the two patients who recovered (Cases 1 and 3) and in another who died (Case 10) there were fluctuating T-wave inversions, mostly in right chest leads (see Fig. 1). In Case 10 it is possible the fluctuating T inversion in V4 was due to slight alteration in location of the electrodes. But as the records were all taken by the same technician under the supervision of one of us (H. A. R.) and as unequivocally abnormal changes occurred in other patients, we think this explanation unlikely. The position of the patient was also investigated as a factor in causing pattern changes. Consecutive records were taken with the patient lying flat on his back, on the left, and then the right side. There was no significant difference between the records. In Cases 2 and 5 the E.C.G.s became progressively and grossly abnormal (see Fig. 3). In Case 2 the record taken 15 minutes before death showed wide biphasic complexes (see Fig. 2).

## Pathology

In Malaya, owing to religious and social customs, it is difficult to obtain consent for necropsies. Permission, however, was granted in Cases 2, 5, 7, and 10. In Case 2 there was slight lung oedema and in Case 10 a diffuse purulent bronchopneumonia. The heart was macroscopically normal in both cases, but microscopy was not done. In Case 5 macroscopic and microscopical findings were not remarkable. No significant histological abnormality was seen in the myocardium or lungs. In Case 7 the uterus was enlarged, but other viscera, including the lungs, appeared normal to the naked eye. Histologically there were inflammatory and necrotic changes in the decidua of the uterus. The brain appeared normal. The liver showed moderate fatty degeneration. In the myocardium there was oedema of the interstitial tissue with a scanty cellular infiltration of mononuclear cells and a few plasma cells. Some of the small nerves were degenerated and infiltrated by the same cells. There was necrosis of a few muscle fibres, the cellular reaction to this being very slight. Dr. A. T. H. Marsden remarked that the acute toxic myocarditis was similar to that found in diphtheria (see Fig. 4).

## Discussion

Two vital factors in tetanus are often overlooked—the toxin dose and the speed with which it becomes fixed to susceptible structures. Payling Wright (1958) has reminded us of animal assays showing a thousand or more lethal doses of toxin in the tissues surrounding the wound. He remarks that in man, who ranks among the more highly susceptible mammals to tetanus, the same great excess may be present. E. A. Wright (1954) showed experimentally that tetanus toxin was rapidly fixed to cells of guinea-pig brain stems. More than half the dose injected was fixed within two hours. Undoubtedly the toxin dose is the paramount factor determining the fate of human victims who have not previously been inoculated with toxoid (and this comprises the great majority of patients in Malaya). In a fortunate minority the toxin dose is small, the illness mild, and the subject recovers with no more treatment than is required to relieve discomfort. In the opposite group the toxin dose is overwhelming and death is inevitable. A third category remains in which treatment can sway the issue. This category may be divided into moderate cases in which conservative treatment as outlined should succeed and severe cases in which it will fail. It is in the latter group that we hope T.P.R. might be effective.

For the clinician, however, a major difficulty lies in allocating individual patients to one of these four groups—mild, moderate, severe, or inevitably fatal—so that appropriate treatment may be given with minimum delay. The traditional method of assessing severity by the duration of incubation and onset period may not in our experience (Reid *et al.*, 1958) be reliable in individual cases shortly after admission. Though these two measurements are valuable in retrospective analysis of series of cases, there are exceptions which vitiate their application to the individual patient. Thus we have seen fatal cases with incubation periods of four weeks and onset periods as long as nine days. Patients with incubation periods of only two or three days and onset period as short as 24 hours have recovered uneventfully. We have known a patient die in hospital during the first spasm five days after the onset of symptoms.

Though all cases in the present series were severe by these criteria, with the possible exception of Case 4 (where the onset period was uncertain), we came to rely more and more on accurate observation of hypertonus and spasms as the index of severity. Satisfactory definition of these terms is a fundamental difficulty in tetanus and makes comparison of results in different series treacherous. Both hypertonus and spasms may be generalized or localized, involving one part of the body more than another. The stimulus required to put a muscle or group of muscles into tetanic spasm varies from subject to subject and the duration may be less than a second or more than a minute.

We use the term "hypertonus" to describe the constant background of stiffness, whether involving single muscles such as the masseters a group such as the abdominal or neck muscles, a limb, or the whole body. A "spasm" is a sudden spasmodic increase in muscle tone, localized or generalized, spontaneous or induced, lasting a few seconds or more than a minute. We classify tetanus as mild when there is only hypertonus, moderate when spasms do not stop respiration, and severe when one or more spasms arrest breathing. Though this classification is based on substantial clinical experience, we recognize that it is arbitrary and far from infallible—as instanced by the apparently mild case in which the patient died during the first spasm. We are unable to distinguish the inevitably fatal from the severe in the early stages. But we think a spasm stopping respiration despite conservative treatment is the most reliable indication for adopting T.P.R.

The use of T.P.R. was based on the assumption that tetanus killed through the direct or indirect effects of hypertonus and spasms; that tetanus is a self-limiting disease from which the patient will recover if he can be kept alive until the disease burns itself out.

Originally we did not think tetanus toxin affected vital structures other than motor-nerve cells. However, with T.P.R. one can prolong survival and see further effects of tetanus emerging. We now believe there is a direct action on the myocardium.

We think the two patients who recovered (Cases 1 and 3) would have died if we had persisted with conservative treatment, and that T.P.R. was effective in saving their lives. It might also be regarded as effective in Case 10, as the tetanus toxaemia was waning when the patient died from lung infection 10 days after stopping T.P.R.

The results in the remaining seven patients can only be described as disappointing. Was the toxin dose so overwhelming that death was inevitable? The common feature in these cases has been the development of hypotension two or five days after the start of T.P.R. This has usually occurred when all was going well. In Case 2 the hypotension persisted for four days until death, but in the other cases it was episodic, lasting half to several hours. All the patients except in Case 6 died in a hypotensive phase. It seems unlikely the treatment was responsible. The extensive experience gained in western Europe from the treatment of respiratory insufficiency in poliomyelitis by I.P.P.R.—often for months at a time—shows without doubt that man can accommodate himself to this regime if it is properly managed. We do not think that technical mismanagement was an important factor in our bad results. Theoretically, I.P.P.R. may diminish return of blood to the heart by increasing the pressure in the chest. It might be thought that this mechanical factor rather than the tetanus toxin was responsible for the hypotensive phases. But hypotension did not occur in two patients recovering, and they were subjected to I.P.P.R. longer than the other three patients.

Secondly, the introduction of a negative-pressure phase in the last five cases did not prevent hypotension. Heavy sedation may be a contributory factor in the deaths of tetanus patients. But in later cases we have not given sedatives. Yet lethal hypotension still occurred. Foldes (1957) showed that excretion of D-tubocurarine may be slow. The initial recovery from its effects is due to a redistribution through extracellular spaces, and the ultimate elimination proceeds slowly, by renal excretion and liver action. With continued administration a point of saturation might be reached after which the plasma concentration would rapidly rise. Depression of vital centres might then result if there is concomitant electrolyte upset. But in the two patients receiving the most prolonged D-tubocurarine administration (Cases 1 and 3) recovery ensued without hypotension. Furthermore, no biochemical or E.C.G. evidence of significant electrolyte upset was observed.

An important observation in Case 4 was the effect of intravenous digoxin—the blood-pressure promptly rose from 80/50 to 110/90, though no vasoconstrictors were given. According to Goodman and Gilman (1955) digitalis affects systolic blood-pressure largely by its action on the heart and not by any significant effect on the blood vessels or vasomotor centre. In Case 2 noradrenaline raised the diastolic blood-pressure to a normal level yet the systolic blood-pressure remained low. To maintain this partial response steady increase in dosage was necessary until enormous amounts had to be given—30 drops a minute of a solution with 192 mg. per 540 ml. These observations suggest the hypotension was due to central myocardial failure rather than to peripheral arteriolar relaxation. Fluctuating irregularities of the pulse and the E.C.G. findings support this concept. Whenever an E.C.G. was taken during the hypotension it was abnormal.

In Cases 2 and 5 the records became progressively abnormal. At necropsy in Case 5 the myocardium was histologically normal. This, of course, does not exclude lethal biochemical changes. In Case 7, however, microscopy revealed an acute toxic myocarditis. Lassen *et al.* (1954) recorded histological evidence of myocarditis in one of their four patients treated by I.P.P.R. But the patient had septicaemia, and the myocarditis might well have been caused by this rather than by the tetanus toxaemia. In Cases 5 and 7 there was no clinical or post-mortem evidence suggesting significant infection other than tetanus. We conclude that the myocardium may be directly damaged by the toxin in severe tetanus. This effect may nullify therapeutic measures such as T.P.R. But not necessarily so: there were E.C.G. changes in both our patients who survived, and in one of the cases reported by Lassen *et al.* (1954) the patient had E.C.G. changes of supraventricular paroxysmal tachycardia yet recovered.

As a result of our experience we consider T.P.R. is indicated in cases of severe tetanus but that in such cases it will be effective to only a limited extent. It will save a few patients who would die if treated by more conservative methods. However, we are as yet unable at the outset to distinguish the patients who may be saved from the ones with a higher toxin dose where death is inevitable.

## Summary

Tetanus may be mild, moderate, severe, or inevitably fatal. Our clinical experience suggests it may be classified as severe (or, maybe, inevitably fatal) when a tetanic spasm stops respiration.

Ten patients with severe tetanus were treated by the total paralysis regime (T.P.R.), consisting of tracheostomy, curarization, and intermittent positive- or positive/negative-pressure respiration. Two of the patients were saved by T.P.R. and therefore only limited effectiveness can be claimed for the regime.

In inevitably fatal cases survival can be prolonged by T.P.R. so that further effects of tetanus toxin emerge. Of these, the most important appears to be direct damage to the myocardium.

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# THE LENGTH OF THE HUMAN UMBILICAL CORD

## A STATISTICAL REPORT

BY

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### Introduction and Theory

Not the least of several intriguing features of the human umbilical cord is its length. This varies considerably, but the most usual length is 20–22 in. (50–56 cm.) (Gardiner, 1922). Most textbooks (see Gibberd *et al.*, 1956) follow Gardiner in asserting that a cord nearly 14 in. (35.5 cm.) long is necessary for normal delivery. It is to be expected that a relatively long cord would often be coiled round part of the body, usually the neck. Gibberd *et al.* (1956, p. 172) claimed that this happened in about 30% of all deliveries. Furthermore, we are taught that the midwife should uncoil or cut such a cord in order to make delivery safe.

There are two points to note. First, all experienced obstetricians must have seen a normal spontaneous delivery with a cord less than 12 in. (30 cm.) long. Secondly, many of them will agree with Thomas Denman (1816) that, if the child is alive when the head is born with the cord round the neck, mother and child may be safely delivered without uncoiling or cutting the cord owing to the descent of the fundus.

In order to establish the range of cord lengths compatible with normal delivery we asked the midwives of the Cambridge Maternity Hospital, with the kind permission of the senior obstetric consultant and the matron, to measure the cord lengths of children born in the hospital from August, 1957, until January, 1958. The cords were measured with a steel rule, 2 feet (61 cm.) long when extended, within half an hour of delivery. It is the practice in this hospital to cut the cord about 3 in. (7.5 cm.) from the umbilicus, so that at least two measurements were made for each cord length.

The cord lengths varied between 7 and 48 in. (17.8 and 121.9 cm.), the mean being 21.3 in. (54.1 cm.). Spontaneous delivery of normal children occurred with any length of cord. The cord was noted to be coiled round the neck in 17% of the cases.

If normal gestation and parturition can occur with any cord length from 7 to 48 in. (17.8 to 121.9 cm.) why is the cord usually more than 20 in. (50.8 cm.) long?

Observations on other mammals are scanty, but there is evidence that man shares with primates a relatively long cord. Starck (1957) found a chimpanzee, admittedly premature, with a cord over twice the crown–rump length of the foetus. Fox (1929) gives accounts of the births of live anthropoid apes. In an orang-outang the cord was 60 cm. (23.6 in.) long, and in a chimpanzee the cord was round the neck and was 49 cm. (19.3 in.) long.

In most mammals the umbilical cord is reasonably well adapted to the immediate post-natal requirements of mother and child. We suggest that, while the length of the cord is, within wide limits, unimportant for gestation and parturition, there may be an advantage immediately after the birth of the child in having a long cord. We submit the theory that the human cord is long in order to allow the mother to pick up her helpless newborn child and carry it away from danger without exerting harmful traction on the placenta. Further, that a cord of more than 18 in. (46 cm.) will allow the child to be put to the breast with the placenta *in utero* and that the reflex stimulation of suckling may promote an easy and bloodless third stage.

We therefore extracted from the case sheets of 223 mothers, consecutive deliveries over a period of about one month, facts about the mother and child, such as age, parity, height, weight, blood group of mother: lengths of the three stages of labour; normal or abnormal haemorrhage; normal or abnormal labour: sex, length, and weight of child; maturity of child: and the cord length. In this way we hoped to discover whether there was any correlation between cord length and the various facts abstracted. For instance, it might be argued that if the third stage of labour was very short there would not be the same need for a long cord: very tall women might be expected to bear children with cords longer than the average, and so on.

### Results

The cord was measured in 177 of these 223 births (79.4%). Fig. 1 shows the distribution of the 177 cord lengths. A histogram of the distribution of all cord lengths collected between August, 1957, and January, 1958, has an almost identical shape.

None of the following factors seemed to affect the length of the cord, except possibly the sex of the child.

*Parity.*—Mean number of previous pregnancies, between 1 and 2; range, 0 to 9.

*Age of Mother.*—Mean, 26 years; range, 16 to 44 years.

*Blood Group of Mother.*—Group A, 39.5%; group O, 39.5%; group B, 9.0%; group AB, 5.1%; no result, 4.0%; not recorded, 2.9%; rhesus-positive, 72.3%; rhesus-negative, 18.6%; rhesus-negative with antibodies, 2.8%; unknown, 6.3%.

*Height of Mother.*—Mean, 63 in. (160 cm.); range 57–71 in. (145–180 cm.).

*Weight of Mother.*—Mean, 136 lb. (61.7 kg.); range, 91–217 lb. (41.3–98.4 kg.). These weights are unreliable, as some women were several months pregnant when weighed.

*Pre-eclamptic Toxaemia.*—The blood-pressure, the condition of the urine, and changes of weight are tests for

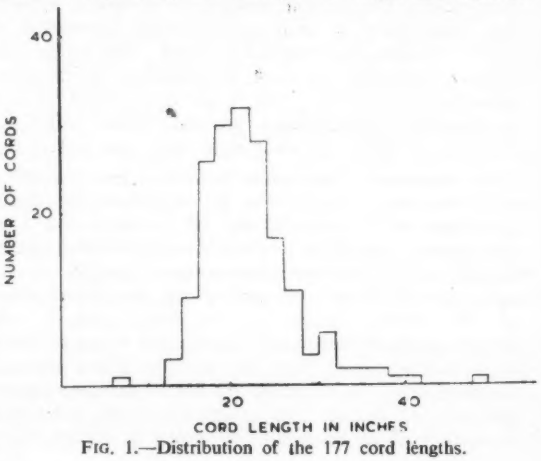


FIG. 1.—Distribution of the 177 cord lengths.

pre-eclamptic toxaemia. The findings were as follows: abnormal blood-pressure, 24.7%; abnormal condition of urine, 7.7%; abnormal changes of weight, 12.9%.

*Duration of Pregnancy.*—Mean, 39 weeks; range, 28 to 42 weeks. The mean cord lengths are given in Table I.

TABLE I.—*Duration of Pregnancy and Corresponding Mean Cord Length*

| Duration of Pregnancy in Weeks | Number | Mean Cord Length | |
|---|---|---|---|
| | | in. | cm. |
| 28 | 1 | 17·0 | 43·2 |
| 32 | 2 | 22·0 | 55·9 |
| 34 | 1 | 19·0 | 48·3 |
| 35 | 3 | 17·7 | 44·9 |
| 36 | 5 | 18·8 | 47·7 |
| 37 | 6 | 23·2 | 58·9 |
| 38 | 20 | 23·3 | 59·2 |
| 39 | 23 | 21·5 | 54·6 |
| 40 | 67 | 21·1 | 53·6 |
| 41 | 28 | 20·7 | 52·6 |
| 42 | 17 | 22·2 | 56·4 |
| Unknown | 4 | 19·8 | 50·3 |

*Presentation.*—Mean cord length of breech presentations, 17.5 in. (44.5 cm.); mean cord length of vertex presentations, 21.4 in. (54.3 cm.). A breech presentation at delivery occurred in 4 cases out of 177: it appears to be associated with a shorter cord. As three of these breeches were complicated by extended legs, which made them difficult to turn, and the fourth was a very small child, we are unable to draw any conclusions from this finding.

*Circumvolution of Cord.*—The 13 cords which were cut during delivery had a very slightly longer mean length. The mean cord length seemed to increase slightly according to whether the position of the cord was normal, round the neck once, or round the neck twice. The findings were: Cord normal, 142 cases; cord round neck once, 24 cases; cord round neck twice, 3 cases; other abnormalities 3 cases. The mean cord length of the last three was 30.7 in. (78 cm.). Two of these abnormalities were true knots in the cord, and in the other the cord was loosely round the body.

Blood loss.—This was abnormal in 10.2%.

*Sex.*—Males numbered 87, with a mean cord length of 22.2 in. (56.4 cm.), and S.E. of ±0.66 in. (1.68 cm.). Females numbered 90, the mean cord length being 20.5 in. (52.1 cm.), with S.E.±0.49 in. (1.24 cm.). It seems that male children have slightly longer cords at birth than female children.

*Stillbirths.*—Mean cord length of live births, 21.5 in. (54.6 cm.); mean cord length of stillbirths, 17.3 in. (43.9 cm.). Mean duration of pregnancy of stillborn, 34.5 weeks; range of duration of pregnancy of stillborn, 28 to 39 weeks; mean duration of third stage of labour of stillborn, 10 minutes; mean weight of stillborn, 3.8 lb. (1,725 g.). The six stillbirths included two cases of toxaemia, one case of the cord once round the neck, and another with the cord twice round the neck. All the stillborn were females.

*Abnormal Birth.*—10.2% of the children were abnormal.

*Weight of Child.*—Mean, 7.2 lb. (3,265 g.); range, 1.5 to 10.3 lb. (680–4,670 g.).

*Length of Child.*—Mean, 20 in. (50.8 cm.); range, 12–22 in. (30.5–56 cm.).

*Labour.*—Mean duration of first stage, 10.7 hours; range of duration of first stage, 1 to 45 hours; mean duration of second stage, 42 minutes; range of duration of second stage, 0 to 3.5 hours; mean duration of third stage, 12 minutes; range of duration of third stage, 0 to 60 minutes. The mean cord lengths for the duration of the third stage of labour are given in Table II.

Our hypothesis was that the duration of the third stage of labour is related to the cord length, and this cannot be seen from the results so far obtained. To investigate this theory more closely, a multiple linear regression of cord length was done on nine factors which were thought to have the greatest bearing on the cord length, the duration of the third stage of labour coming last. These factors are listed in Table III. The mothers were classified into two groups for parity—primigravida and multigravida—as it was not thought that the number of previous pregnancies, if one or more, would affect the cord length. This form of analysis was chosen in case a relation between the cord length and the duration of the third stage of labour was concealed by one of the other factors.

TABLE II.—*Duration of the Third Stage of Labour and Corresponding Mean Cord Length*

| Duration of 3rd Stage of Labour in Minutes | Number | Mean Cord Length | |
|---|---|---|---|
| | | in. | cm. |
| <12 | 71 | 21·3 | 54·1 |
| 12– | 67 | 21·1 | 53·6 |
| 18– | 24 | 22·0 | 55·9 |
| 24+ | 13 | 19·5 | 49·5 |
| Unknown | 2 | 31·5 | 80·0 |

To take a hypothetical example of a 2-factor case: suppose a linear relationship exists between cord length and duration of the third stage of labour, but that male children have longer cords than female children. In Fig. 2A no relationship can be seen to exist between the cord length and duration of the third stage of labour. However, taking the correlations between cord length and sex and between the duration of the third stage of labour and sex into account, as in Fig. 2B, a relationship can be seen to exist. Thus, if a relation between the cord length and the duration of the third stage exists it may be concealed by one of the other factors stated in Table III.

To perform this analysis so as to ascertain whether there is such a relationship it is necessary to restrict the population still further by excluding all cases with missing records of any of the nine factors, and also all cases where mother or child were abnormal. The number remaining was 84 (37.7% of the original number); 51.1% were omitted because of missing records and the remaining 11.2% through abnormalities. The large number of abnormal cases was expected, because these are more likely to be admitted to hospital.

The distribution of cord lengths and the frequencies for the nine chosen factors are not

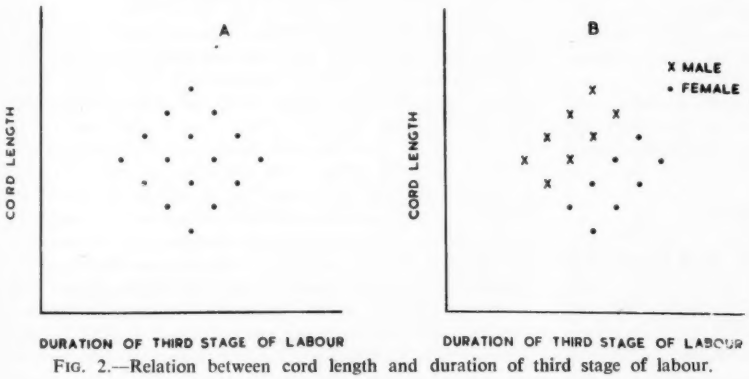


FIG. 2.—Relation between cord length and duration of third stage of labour.

significantly affected by this selection. Indeed, for some factors, notably sex, it is a better selection of the 223 cases than the original selection of 177 measured cord lengths. However, there seems to be a deficiency of mothers over the age of 35 years, and of children born before 38 weeks of pregnancy.

From Table III it can be seen that the duration of the third stage of labour does not significantly affect the length of the cord. Two of the sums of squares were significantly small. This is reasonable, since two other sums of squares were quite large, though not significantly so.

A linear regression was performed of cord length on each factor in turn, and none of the factors was found to be significant. Sex seemed to affect the cord length most, male children having slightly longer cords.

TABLE III.—*Analysis of Variance Table for Multiple Linear Regression of Cord Length*

| Source | Degree of Freedom | Mean Square | P |
|---|---|---|---|
| Regression on sex | 1 | 63·266 | 0·30>P>0·10 |
| ,, ,, weight of mother after above factor | 1 | 31·025 | 0·30>P>0·10 |
| Regression on height of mother after above factors | 1 | 0·022 | 0·99>P>0·975 |
| Regression on length of child after above factors | 1 | 4·875 | 0·70>P>0·50 |
| Regression on duration of pregnancy after above factors | 1 | 4·822 | 0·70>P>0·50 |
| Regression on weight of child after above factors | 1 | 21·418 | 0·50>P>0·30 |
| Regression on parity after above factors | 1 | 6·875 | 0·70>P>0·50 |
| Regression on age after above factors | 1 | 0·013 | 0·99>P>0·975 |
| Regression on duration of 3rd stage of labour after above factors | 1 | 2·217 | 0·90>P>0·70 |
| Residual | 74 | 28·311 | |

## Other Results

Since a linear regression of cord lengths on duration of pregnancy was not statistically significant, there is no evidence that cords grow in length after 28 weeks of pregnancy.

A linear regression of height of child on duration of pregnancy was done for each sex in order to test the hypothesis that girls stop growing after the 38th week of pregnancy while boys continue to grow. The regression was significant in both cases; thus both boys and girls continue to grow throughout the pregnancy. The slope of the regression line was slightly greater for boys than for girls, though the difference was not significant.

In 200 mothers (89.7% of the cases) the blood groups were recorded and the figures for each group were compared by means of the $\chi^2$ test with the corresponding ABO figures for the United Kingdom (Dobson and Ikin, 1946) and Rh figures (Mollison *et al.*, 1952). $\chi^2$ was not significant in both instances. ($0.10<P<0.25$). Thus the Cambridge data do not differ from national figures.

In 82 out of the 84 complete records, blood groups were recorded. When compared with the ABO and Rh frequencies the $\chi^2$ test was again not significant in both cases ($0.25<P<0.50$).

## Summary and Conclusions

Maternity records were collected of mother and child and of umbilical cord length at a Cambridge hospital and the data were analysed. It was found that normal gestation and delivery can occur with any length of cord between 7 and 48 in. (17.8 and 121.9 cm.).

In the sample of population examined, which is probably fairly typical of the population in this country, there is no evidence that any of the factors which were thought to be relevant are related to cord length.

Though our results are largely negative, we present this paper for two reasons. First, it demonstrates how, from a small number of easily collected data, it is possible by statistical analysis to arrive at fairly definite conclusions. Secondly, we feel that the data collected and analysed may be used for comparison with data from other populations.

It is interesting that the analysis shows that while male and female children continue to grow throughout pregnancy there is no evidence of growth in cord length after 28 weeks. This is not surprising, as the placenta begins to degenerate about this time.

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# RESULTS OF TENOTOMY OF THE TENDO ACHILLIS IN INTERMITTENT CLAUDICATION

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Operations carried out solely for the relief of symptoms without rectifying in any way the underlying cause of those symptoms have never been widely practised by British surgeons. With the exception of procedures to alleviate the misery of advanced malignant disease, purely symptomatic surgery tends to be regarded as quackery, and those who practise it to be relegated to the fringe of, if not well within, the underworld of surgery. It is illogical, however, to deny a patient relief of his discomfort simply because the underlying cause is either unknown or impossible to rectify.

Intermittent claudication is an excellent example. With the exception of the very few patients suitable and fit for arterial reconstruction there is little to offer the mass of sufferers from this crippling symptom. Sympathectomy has its place as a limb-preserving procedure, but it contributes little, as a rule, to the relief of their exercise pain. An attempt was made in 1947 to relieve exercise pain confined to the gastrocnemii by division of the branches of the popliteal nerves supplying these muscles. This operation, however, proved unsatisfactory for several reasons. It was necessary to be certain that the soleus was not involved in the production of pain; isolation of the branches to the gastrocnemii was not always an easy matter; and finally it was necessary to keep the patient in bed for several days, as a result of which venous thrombosis in the paralysed

muscle-bellies was a frequent and trying complication. In order to widen the scope so as to include the soleus and minimize the period of recumbency, it was decided to try defunctioning the calf muscles by tenotomy of the tendo Achillis. The complete relief of pain and the very slight degree of disability resulting from this procedure seemed at first to have solved the problem. It was soon found, however, that the selection of patients suitable for this minor procedure was by no means easy. This short paper, somewhat overdue, we fear, is based on our experience of this operation in 72 patients.

### Technique of Subcutaneous Tenotomy of the Tendo Achillis

This simple operation is much easier to demonstrate than to describe. With the patient under general anaesthesia, the limb, flexed to a right angle at the hip and knee, is held firmly by an assistant standing on the outer side (see Fig.). The assistant grasps the forefoot with one hand to maintain dorsiflexion and supports the calf with the other. The limb is held firmly in the correct position by clasping it between the upper arm and the body. The skin in the area of operation is prepared in the usual way and isolated by sterile towels. The assistant, who plays a vital part in the success of the operation, dorsiflexes the foot to render the tendo Achillis taut. The surgeon stands opposite the assistant, on the inner side of the limb, and inserts the tenotome immediately in front of the tendon about 1 in. (2.5 cm.) above the os calcis, where the tendon is narrowest and almost cylindrical. By division at this level the bursa between the tendon and the bone is avoided. The tendon is then gradually divided by a sawing movement, the assistant steadily increasing dorsiflexion of the foot to keep the tendon taut. At the moment of division of the final strands of the tendon the assistant must relax pressure on the foot or the skin may split. The gap between the divided ends of the tendon is compressed between gauze swabs for a few moments to control bleeding. The assistant then dorsiflexes the foot again in order that the surgeon may verify the completion of division. If any fibres are found to be undivided, the tenotome is reinserted and division completed. A firm crêpe bandage is then applied over a pressure dressing of gauze and wool.

Position of leg and assistant for tenotomy of tendo Achillis.

### Aftercare

The key to success lies in careful post-operative management and the patient's intelligent co-operation. The patient must be urged to walk as soon as possible and to concentrate on walking with a normal gait. After 24 hours the wound is inspected, and if satisfactory the patient is encouraged to walk. At first it is wise to sit the patient on the edge of his bed with his feet on the floor, gradually increasing the pressure on the tenotomized foot until he feels confident enough to stand up He should be supported until he feels comfortable and is able to stand normally. He should be encouraged to repeat this manœuvre by himself until he feels quite stable before trying to walk. It is very unwise to try to make him walk until he can stand with confidence. The nervous patient may not get further than repeating the exercise of standing by his bed on the first day. As soon as he is able to stand comfortably and maintain his balance walking should be encouraged, at first with support, then alone with the aid of a stick. In a day or two he should be able to walk unaided. The first few steps are usually painful, but as the stiffness wears off the pain rapidly eases. Walking should be painless and the patient able to resume his normal life within a week or so after operation.

After division the ends separate, forming a gap of about 2 in. (5 cm.), which is maintained by use of the leg. After a few months the gap is bridged by a band of tissue—probably tendinous, though its histology has never been investigated—which thickens. Moderately strong plantar flexion becomes possible. This band does not usually contract and does not approximate the cut ends, so the tendon is permanently lengthened. If the patient is kept in bed the ends remain in apposition and heal without lengthening.

### Complications of the Operation

Early complications are haematoma with persistent leakage of serosanguineous fluid from the wound, leakage of clear bursal fluid, and infection. With these complications walking is delayed. Phlebitis in the defunctioned muscles may follow, leading to further delay in ambulation and reunion of the tendon without lengthening. This occurred in two patients amongst our 41 complete failures.

A more usual cause of immediate rejoining of the tendon without lengthening was the refusal of the patient to persevere in his walking after the operation. This applied to three of the four patients on whom tenotomy was carried out while they were out-patients. As supervision did not extend to their post-operative exercises, these were not performed, and the tendon immediately rejoined. Two other patients took to their beds after their return home and a junction occurred. All these patients were of rather low intelligence, in whom the desire to walk was not supported by sufficient determination.

The principal late complication is a sore heel. About 40% of the patients complained of some degree of discomfort in the heel. Discomfort in walking due to a tender heel seems to come on about three to four weeks after the resumption of normal activity. A plastic foam pad under the heel gives relief, and the discomfort gradually diminishes, usually disappearing completely in a few months. In two patients the tenderness was persistent and severe. Complete relief followed division of the posterior saphenous nerve in the back of the calf. In some cases the area of tenderness in the heel is localized and an *x*-ray film reveals a typical calcanean spur. It seems probable that the discomfort is caused by the rather "pounding" gait after tenotomy in patients who have lost some of the normal fatty pad on the plantar surface of the heel. Recovery after some months is due to rejoining of the tendon, leading to a more normal "springy" gait and less trauma to the heel.

After operation the patient walks with a limp; but this improves as the tendon rejoins with lengthening.

## Results

Tenotomy of the tendo Achillis was carried out in 72 patients, in 10 of whom both tendons were divided. The majority fell into the 55–64 age-group (Table I). They were all severely handicapped by claudication and were mostly grade 3 or late grade 2 (Boyd *et al.*, 1949).

TABLE I.—*Ages of the 72 Patients Tenotomized*

| Age in years | 33–45 | 45–54 | 55–64 | 65–74 |
|---|---|---|---|---|
| No. of patients | 1 | 5 | 52 | 14 |

TABLE II.—*Results of Tenotomy*

| | Unilateral | Bilateral | Total |
|---|---|---|---|
| Complete relief | 14 | 2 | 16 (22%) |
| Initial relief with late failure | 14 | 1 | 15 (21%) |
| Immediate failure | 34 | 7 | 41 (57%) |
| Total | 62 | 10 | 72 |

TABLE III.—*Causes of Failure*

| | Unilateral | Bilateral |
|---|---|---|
| Late failure after initial relief | 14 | 1 |
| Intermittent claudication in other leg | 6 | |
| Osteoarthritis | 4 | 1 |
| Intermittent claudication in same leg due to rejoined tendon | 4 | |
| Immediate failure | 34 | 7 |
| Amputation of either leg | 6 | |
| Osteoarthritis | 4 | 2 |
| Intermittent claudication in other leg | 12 | |
| ,, ,, ,, same ,, : | | |
| Thigh | 4 | 2 |
| Anterior tibia | 1 | |
| Tendon rejoined | 6 | 1 |
| Instability | | 2 |
| Painful state | 1 | |

Complete relief of pain, enabling the patient to walk without discomfort as far as he desired, resulted in 16 patients (22%) (Table II), including two in whom both tendons had been divided. The longest period of relief was 10 years, the patient walking without pain until her recent death. The average length of the follow-up to the patient's death, to the onset of ischaemia requiring amputation of one or other leg, or to the present day is 4.5 years.

Temporary relief lasting not less than a year occurred in a further 15 patients, including one in whom both tendons had been divided. Failure in these cases was due to the onset of intermittent claudication in the other leg in six patients, and in the tenotomized leg in four patients whose tendons rejoined and, by gradual shortening, eventually had inadequate length to prevent use of the muscle (Table III). The other five patients developed pain due to osteoarthritis, with limitation of walking.

There were 41 patients who never benefited from the operation, seven of whom had bilateral operations. In patients tenotomized bilaterally one failure was due to the patient going to bed on returning home, when the tendons rejoined. Two were due to the inability of the patient to balance while walking or standing. A further two had intermittent claudication in the thigh after the operations. Two developed arthritic pain. In the 34 unilateral operations, six patients failed to benefit because of the onset of gangrene in one or other leg shortly after the operation. In 12 cases intermittent claudication was revealed in the other leg, and five had intermittent claudication in the leg operated upon, either in the thigh or the anterior tibial group of muscles. One patient had a painful state of the foot and ankle which was due to too tight bandaging after tenotomy but which did not lead to amputation. Four developed arthritic pain. A further six failures have already been discussed, being due to the immediate rejoining of the tendon.

## Discussion

Though only 22% had lasting relief, a further 21% had a worth-while respite of a year at least. Of the 41 patients who did not benefit, five were probably unsuitable owing to their mental outlook and non-persistence with walking. Six immediate failures due to the precipitation of osteoarthritis were the results of poor selection. In another 17 patients intermittent claudication in the same or the other leg was the cause of failure and also reflects upon the selection. We now feel that bilateral tenotomy should only rarely be done and therefore a further six patients should be added to the list of failures. This totals 24 patients out of 41 who probably should never have been tenotomized. It has been suggested that the success of tenotomy is due to slowing of the patients' walking pace. Those whom we have operated on have all been persons whose pain was so severe that their pace had already been slowed to the minimum compatible with useful activity. The improvement which occurs is a real one.

The overall picture strongly suggests that tenotomy has a place in the palliative treatment of intermittent claudication provided that patients suitable for the operation are very carefully selected.

## Selection of Patients

No hard-and-fast rules can be laid down. The selection must be entirely individual. The nature and purpose of the operation must be carefully explained to the patient, and so must the possibility of disappointment and the reasons for it.

Success depends very largely on the patient's intelligent, determined, and courageous co-operation. Only subjects with the right outlook should be considered. The claudication must be confined to the calf and should be grade 3 in our clinical grading. In clinical grade 3 the exercise pain increases rapidly in severity until the patient is forced to stop. Owing to the marked tendency to spontaneous improvement in patients who have had a recent thrombosis of a main vessel, grade 3 patients with a recent onset of claudication should not be operated on until their non-improvement is certain. The nutritional state of the limb must be good enough to give no grounds for anxiety in the near future.

Aortico-iliac thrombosis which is causing only calf claudication may, if the patient is tenotomized, lead to thigh and buttock claudication. Patients with this lesion should therefore be excluded.

The two main causes of disappointment we found after tenotomy were intermittent claudication in the opposite limb or in other muscle groups in the same limb, and osteoarthritis.

Reference to the causes of failure (Table III) shows that almost half the patients with unilateral tenotomies (27 out of 48) suffered immediately or later from claudication in the opposite limb or in the same limb. Approximately one-fifth of the patients with segmental thrombosis will suffer a second thrombosis in the same or the opposite limb within five years from the onset of their claudication. This hazard of later thrombosis is unavoidable, but every effort must be made to exclude those patients in whom claudication in the thigh or other leg is almost certain to occur. It is often very difficult to assess the degree of impairment of the

circulation in the opposite limb and whether or not it is severe enough to be likely to cause discomfort at an uneconomic distance. The only certain way to solve the problem of whether either leg will be responsible for immediate failure after tenotomy is by employing the Hunterian method. The patient is walked until he is halted by claudication in the leg on which tenotomy is contemplated. Claudication is then abolished by blocking the nerve supply to the gastrocnemius and soleus with lignocaine and the patient is walked again. With relief of pain in the group on which tenotomy is under consideration, the behaviour of the limbs on exercise can be studied.

*Osteoarthritis.*—It is not surprising to find degenerative changes in joint cartilage in the age period in which degenerative changes in arteries are most often present. Osteoarthritis in the knee-joint is not uncommonly a co-partner with arteriosclerosis in limiting a patient's activity. A minor degree of arthritis may pass unnoticed in a patient whose walking is severely reduced by intermittent claudication. If, however, the claudication is relieved, permitting increased activity, the hitherto quiescent arthritis may become an even more intractable disability than the claudication. It is very disappointing to find that the calf pain which hitherto limited walking to 200 yards (183 metres) is replaced by an equally crippling discomfort at 300 yards (274 metres). The risk of such an occurrence is particularly great after tenotomy of the tendo Achillis on account of the slight degree of instability of the knee following defunctioning of the gastrocnemius. Tenotomy may convert a subclinical degree of osteoarthritis of the knee-joint, hitherto painless, into a crippling disability by depriving the joint of the postural support of the gastrocnemius muscle. One-third of our late failures were due to osteoarthritis. In some patients the onset of osteoarthritis is unpredictable, but probably half of our failures due to osteoarthritis could have been avoided by more careful selection.

*Bilateral Tenotomy.*—Owing to the possibility of instability and thigh pain we feel that this should very rarely be done. It should certainly not be done with only a short interval between the two operations. We feel that a possible indication may be the late occurrence of calf pain in the other leg of an already tenotomized patient, whose previously sectioned tendon has rejoined sufficiently to allow him some moderately powerful plantar flexion on that side.

*Angina, Emphysema, and Bronchitis.*—Disappointment after alleviating exercise pain in the calf muscles is not infrequently due to breathlessness from bronchitis or emphysema, or anginal pain limiting activity. As it happens, we have no examples of either of these conditions in our series of tenotomies, though this unfortunate sequel has been seen after relief of claudication by other means. Great care, therefore, should be taken to exclude, so far as possible, patients in whom there is a risk of these conditions limiting activity.

In practice the decision for or against tenotomy is made by weighing the likelihood of further arterial insufficiency against the patient's desire to walk and his willingness, after being fully informed of the hazards, to accept the risks of failure. With careful selection our recent results have been more pleasing. In our last eight patients, five have had complete relief, with an average follow-up period of three years. There were no immediate failures; but we had three late failures, due to osteoarthritis in two and to intermittent claudication in the other leg in one.


### Summary

Our experience of subcutaneous tenotomy of the tendo Achillis for the relief of intermittent claudication in 72 patients is discussed.

The technique of this simple procedure is described and the complications of the operation are discussed.

The results, tabulated under three headings, were: (*a*) complete relief in 16 (22%), including two bilateral tendon sections; (*b*) temporary relief—minimum of one year—in 15 (21%) including one bilateral tendon section; and (*c*) immediate failure in 41 (57%) including seven bilateral tendon sections.

The causes of failure are discussed in detail. Immediate failures were due to intermittent claudication elsewhere in the same leg or in the opposite leg; these constitute approximately 50% of the failures. The remaining 50% were divided almost equally between early union of the divided tendon without lengthening, onset of ischaemic changes leading to amputation, and osteoarthritis.

We feel that this high failure rate (57%) could have been greatly reduced by better selection; 34 out of 41 probably should never have been tenotomized.

The principles of selection are discussed and the difficulties outlined.

In our opinion this operation has a definite though limited place in the management of intermittent claudication.



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## INCIDENCE OF INTUSSUSCEPTION AND CONGENITAL HYPERTROPHIC PYLORIC STENOSIS IN EDINBURGH CHILDREN


BY

**IAN McD. SMITH, M.B., Ch.B.**

*From the Royal Edinburgh Hospital for Sick Children*


Recent comparison of the incidence of acute intussusception in Newcastle upon Tyne (Court and Knox, 1959) and in Birmingham (MacMahon, 1955) has shown a marked difference between the incidence in the two cities, while the incidence of congenital pyloric stenosis in Newcastle upon Tyne (Davison, 1946) and Birmingham (MacMahon *et al.*, 1951) shows a striking similarity. Before any conclusion can be drawn from these figures it will be necessary to carry out similar surveys in other centres, and with this in view a survey has been made of such cases occurring within the City of Edinburgh during the period 1950 to 1958.

### Method

The method used is similar to that employed in the previously reported series (Davison, 1946; Spence and Court, 1950; MacMahon, 1955)—the total number of children with an Edinburgh address admitted to any of the children's units within the city during the nine-year period 1950 to 1958. Again, as in the previous series,

only those cases confirmed by operation or by barium-enema examination have been included, while those classed as " spontaneous reduction " have been excluded.

In the case of congenital hypertrophic pyloric stenosis only cases confirmed by operation or by necropsy (one case) were included in the series. There was, in fact, no record of a medically treated case of pyloric stenosis during the period of the survey, all cases diagnosed being surgically relieved by Ramstedt's operation. This differs considerably from the series reported from Birmingham, in which 83 out of a total of 578 cases were either medically treated or found at necropsy.

### Findings

During the nine-year period 105 cases of intussusception were admitted to the children's units in the city, and, though the rate of admission was on the whole steady, in three of these years there was a marked drop in the incidence despite the fact that the birth rate was essentially unchanged; this being noticed also in the rate of admission of children from outside the city.

From 1950 to 1958 the number of live births in the City of Edinburgh totalled 66,966, thus giving an incidence of intussusception of 1.57 per 1,000 live births. This shows a much lower incidence than that in Newcastle upon Tyne during the period 1950 to 1957—4.3 per 1,000 live births—and is comparable to the incidence in Birmingham of 1.49 per 1,000 live births.

During the same period 205 cases of congenital pyloric stenosis were admitted to the various hospitals, giving an incidence of 3.06 per 1,000 live births. This figure is very similar to those previously reported from Birmingham (3.0 per 1,000 live births) and from Newcastle upon Tyne (2.8 per 1,000 live births).

### Discussion

Despite the fact that there is a considerable difference in the occupation of the inhabitants, conditions of work, density of population, and, to some extent, climatic conditions between the cities of Birmingham and Edinburgh, there is a marked similarity in the incidence of intussusception between the two cities. It may well be that the incidence in Newcastle upon Tyne is unusual in being so high and that the figures for Birmingham and Edinburgh bear a closer relation to the incidence in the country as a whole. It has been suggested that in the Birmingham series some cases which should have been included may have been treated in hospitals on the periphery of the city; this does not arise in Edinburgh, where the city boundary is quite clearly determined.

The striking similarity in the incidence of congenital pyloric stenosis could well be explained by the fact that this condition is not so liable to variance due to population shift as acute intussusception, which is usually later in onset and is, of course, not a congenital disease.

If one accepts that intussusception is more prevalent in the North of England than in the Midlands and in the South, then it might follow that further north the incidence might be even higher. This, however, has not been found to be the case, and the answer may well lie in the more sociological aspects of the cities in which figures have been obtained.

It will be necessary for similar surveys to be carried out in other centres before any concrete conclusion can be drawn from the figures obtained in this series and in those previously reported.

### Summary

An account is given of the incidence of acute intussusception and of congenital pyloric stenosis in the City of Edinburgh; comparison is made with other reported series from Newcastle upon Tyne and Birmingham, and it is found that the incidence of intussusception in Edinburgh (1.57 per 1,000 live births) approximates to that in Birmingham, giving the impression that the incidence in Newcastle upon Tyne is extremely high; on the other hand, the incidence of congenital pyloric stenosis (3.06 per 1,000 live births) is very similar to the incidence in both Newcastle upon Tyne and Birmingham.

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# Reviews

## EARLY DIAGNOSIS

*Early Diagnosis.* By Various Authors. Edited by Henry Miller, M.D., F.R.C.P. (Pp. 400+viii. 25s.) Edinburgh, London: E. and S. Livingstone Ltd. 1959.

This book on early diagnosis is particularly appropriate for the family doctor, for whom it is specifically written. It is the family doctor who sees disease in its earliest phases, and it is in these early and rather vague and indefinite periods that diagnosis is most difficult. The family doctor has to rely almost entirely on clinical acumen to pick up the beginnings of diabetes, cancer, thyrotoxicosis, disseminated sclerosis, and the like. He has to piece together the patient's disjointed history and relate it to the minimum of physical signs, and then finally has to rely on his past knowledge of his patient and on the impressions which all these pieces of evidence create in his mind to make the " diagnosis." He has also to be sufficiently alert to be able to think of possible " organic " diagnoses, which tend to be rare in general practice compared to the many minor and relatively trivial disorders that may present with identical symptoms.

Early diagnosis in practice is essentially a personal and a clinical matter, and as a rule the doctor finds little help from the standard textbooks on his shelves (this is probably why they are so rarely opened and consulted). This book is an exception. Designed for the family doctor, it approaches the problems from highly practical and clinical aspects. In every instance it is the clinical observations that receive the greatest consideration; the importance of a good history and significant, albeit slight, aberrations from the normal receives appropriate emphasis, as do possible early abnormal physical signs. The ancillary investigations mentioned are always those that can be easily carried out by the family doctor, provided he has access to local radiological and pathological departments.

Written by an " all-star " collection of contributors ranging from Lord Cohen through eminent professors and consultants right down to practising family doctors

such as John Hunt and Ian Watson, the 25 chapters cover almost the whole range of systematic medicine and a good deal of surgery, too, for there are five surgical contributors. The material is very well presented, and full of interest even to the most experienced clinician, be he general practitioner or consultant. Everyone who reads this book will lay it down thoughtfully and aware of having picked up a number of useful tips culled from the experience of others. The price is most reasonable, and the production is, as usual, a credit to the publishers.

JOHN FRY.

## CARDIAC ARREST AND RESUSCITATION

*Cardiac Arrest and Resuscitation.* By Hugh E. Stephenson, jun., M.D. (Pp. 378; illustrated. 90s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1958.

"When the great Ice Sheet retreated for the last time about 30,000 years ago, the Cro-Magnon man appeared in Europe and with him the first known origins of medicine and surgery. The Cro-Magnons were an intelligent race of skilful people and keen observers, and in a short time they displaced the brutish, primitive Neanderthal Man. In a pindal cavern a Cro-Magnon artist drew the outlines of a mammoth, and in the center appeared a dark spot which is thought to represent the heart."

These are the opening sentences of a remarkable book, and, though written by Norman Morris, one of the six other contributors, they set the level of interest, style, and knowledge that explode from every chapter. Details are inadequate to describe the value of this book. It is packed with factual information, important and relevant references, practical experience, technical procedures, and sound advice. It is clearly written and printed, and must appeal to all and sundry, not merely to the thoracic surgeons, cardiologists, anaesthetists, and interns to whom one supposes it is particularly addressed. It is also singularly timely, and so far as I am aware nothing quite like it has been written before. That a work so badly needed, and so exquisitely timed, should prove little short of a masterpiece is a miracle. Very few books on medicine, or any other subject for that matter, have given me greater pleasure.

PAUL WOOD.

## HORMONES AND ATHEROSCLEROSIS

*Hormones and Atherosclerosis. Proceedings of the Conference held in Brighton, Utah, March 11–14, 1958.* Edited by Gregory Pincus. (Pp. 484+xiv; illustrated. $13.50.) New York: Academic Press Inc. London: Academic Books, Ltd. 1959.

In this important book there is published a series of papers describing many current investigations into the role of hormones in the genesis and in the treatment of atherosclerosis. These papers with the subsequent discussion represent the proceedings of a conference held last year in the United States. Many distinguished investigators have contributed to this book, and the result is a valuable account of a rapidly developing and complex field of inquiry. Five aspects of the relationship of hormones to atherosclerosis are analysed. In the first section the influence of hormones on cholesterol biosynthesis and katabolism is considered. Second, the role of hormones on lipogenesis and lipid transport, particularly in relation to atheromatous lesions, is discussed. Third, available data on the influence of hormones on experimental atherosclerosis are reviewed. Fourth, the relationship between blood lipids and endocrine function in animals and in man is presented. Fifth, the problems of using hormones in the treatment of hypercholesterolaemia and atherosclerosis is described in detail. This book, admirably edited by Dr. Pincus, will be eagerly read by all concerned with the aetiology and treatment of atheromatous vascular disease.

M. F. OLIVER.

## GERMAN DERMATOLOGY AND VENEREOLOGY

*Dermatologie und Venereologie. Einschliesslich Berufskrankheiten Dermatologischer Kosmetik und Andrologie.* Volume II. Edited by Professor Dr. H. A. Gottron and Professor Dr. W. Schönfeld. (Pp. 1,428+xxxi; illustrated. Part 1: DM. 173; Part 2: DM. 154.) Stuttgart: Georg Thieme Verlag. 1958.

This new German work on dermatology and venereology, edited by two eminent German dermatologists with the collaboration of their numerous colleagues, is to be published in five volumes. The second volume of this handbook has now appeared in two parts. The first chapter deals with the treatment of benign and malignant skin diseases by irradiation. There are excellent chapters about the theoretical and practical aspects of *x* rays, Grenz rays, high-speed electrons, and radioactive isotopes. A chapter on cosmetics will be very useful to any dermatologist who is interested in this particular branch of the subject. One chapter deals with diseases of "still unknown origin." It contains the erythemas, the erythro-squamous eruptions, dermatomyositis, lupus erythematosus, "rheumatism" of the skin, Reiter's disease, vesiculo-bullous eruptions, haemorrhagic eruptions, lichen planus, atrophies, and scleroderma. In another chapter skin diseases due to parasites, fungi, monilia, cocci, bacilli, and viruses are well covered. A chapter dealing with "zoonoses" (diseases occurring in animals and transferred to human beings) gives an excellent account of erysipeloid, brucellosis, toxoplasmosis, tularaemia, glanders, and rat-bite disease (sodoku). The bibliography is extensive, and the print and black-and-white photography are of "Verlag Thieme" standard. Alas, the enormous price of over £30 a volume is not likely to make this excellent work easily available to dermatologists in Great Britain, and it is more likely to become a useful reference book obtainable from a library.

HENRY HABER.

## PHYSIOLOGY OF PHYSICAL FITNESS

*The Clinical Physiology of Physical Fitness and Rehabilitation.* By Ernst Jokl, M.D. (Pp. 194+xvii; illustrated. 63s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

This book includes the essay on clinical physiology for which the author was awarded the Buckston Browne Prize and Medal by the Harveian Society, and it is dedicated to the memory of Sir Charles Sherrington, who is quoted repeatedly. The historical background is filled in with reproductions of illustrations of great men and the title pages of their classic works. Against such an imposing background the rest of the book is disappointing.

One must admire the industry with which Dr. Jokl has collected case reports and physiological data relating to exercise and the state of being trained, and has sought examples of progressive training other than athletic. There is much that is interesting, but little that is new

or provocative. The numerous examples of outstanding performance are impressive testimony, on the one hand, to the body's adaptability to pathological conditions, and on the other to the power of the human will to guide and to drive even the defective to excellence. In his chapter on "Theory and Practice of Rehabilitation," Dr. Jokl indicates how this power may be evoked and reinforced, but he deals only with rehabilitation after disease and does not consider rehabilitation after injury.

As causes of disability disease and injury have much in common, but there is a difference of outstanding importance: most injuries are painful, most diseases are not. Pain figures prominently among the researches of physiologists and clinicians alike and deserves a place in any work on rehabilitation; it is the most influential single consequence of injury, but its manifold influences are rarely given the careful consideration they deserve. Hilton's views on rest and pain were valuable nearly 100 years ago, but they do not justify the present all-too-frequent equation of pain with the need for rest and comfort. The relationship of injury, pain, and disability and the ways of tackling it go far beyond the realm of clinical physiology and rehabilitation, and they deserve better than neglect within it.

P. S. LONDON.

## GRAPHIC EXPRESSION OF MENTAL STATES

*Psychiatrische Themen in Malerei und Graphik.* By Professor Rudolf Lemke, M.D. Edited by Professor Helmut Rennert, M.D. (Pp. 144+vii; illustrated. DM. 31.30.) Jena: VEB Gustav Fischer Verlag. 1958.

The author, who was professor of psychiatry at Jena and a keen amateur painter, died before the publication of this book on "Psychiatric Themes in Painting and other Graphic Arts." He posed the question whether the graphic arts can express qualities of abnormal experiences which language can only inadequately convey. He presents something like a textbook of psychiatry in pictures by famous artists. There is a historical chapter depicting the treatment of the mentally ill. The larger part of the 109 reproductions, of which only two could be printed in their original colours, deal with abnormal mental states, including dreams. Some of the 39 artists whose pictures have been reproduced suffered from mental illness themselves. The author demonstrates that the pictures help in the understanding of symbolic representations of thoughts and feelings, and often give a clearer insight into the world of the mentally ill than language. They also illuminate the relationship between artistic work on the one hand and normal and abnormal fantasy on the other. The book makes enjoyable reading, though it does not contain anything fundamentally new.

E. STENGEL.

## TROPICAL PUBLIC HEALTH

*Public Health in Tropical Countries.* By Oladele A. Ajose, M.D., D.P.H.(Glas.). (Pp. 191+vii; illustrated. 18s.) London: J. and A. Churchill, Ltd. 1958.

This is a book for students, health inspectors, and nurses in the tropics and others interested in the subject. The author also expresses the hope that it may be of value to medical officers. It is written clearly, very simply, and its contents range over the undergraduate curriculum, though there are, as is inevitable, some omissions: rabies, which commonly raises problems in prevention in the tropics, is not discussed, and the now obsolescent use of gentian violet is mentioned in the control of enterobiasis though the more effective piperazine salts are not. Many subjects are dealt with briefly—maternity and child welfare, for example, occupies only 2¼ pages. The book's value must be seen against the background in which it has been written. The author is director of a young and growing Department of Preventive and Social Medicine at University College, Ibadan, Nigeria. A great deal of teaching in the early years of the department—and of similar departments now coming into being elsewhere in the tropics—must be directed towards the training of health inspectors and visitors and the provision of a basic knowledge on which medical undergraduates can build. To this end the book is admirably written and will serve a very useful purpose.

A. W. WOODRUFF.

## DEVELOPMENT OF OPHTHALMOLOGY

*A History of Ophthalmology.* By George E. Arrington, Jr., M.D. Foreword by Félix Martí-Ibáñez, M.D. (Pp. 174+xvii. $4.) New York: MD Publications, Inc. 1959.

The scope of this little book is encyclopaedic. Its 143 pages of text cover the whole development of ophthalmology, beginning with prehistoric times and ending with a chapter devoted to the future. The headings of some of the chapters, such as "Islam and Ophthalmology," "Leonardo da Vinci," "Contemporary Acceleration of Ophthalmic Technology," and "Contemporary Medical Concepts in Relation to Ophthalmology," indicate the author's attempt to relate the development of the specialty to medical history in general and to the history of civilization as a whole. With such a broad scope in such a limited text it is inevitable that the actual events in ophthalmology do not stand out particularly well, and some readers will regret the space allotted to quasi-philosophical discussions.

The history of ophthalmology is one of the most fully documented studies in medical history. There is, therefore, room for short versions in addition to the monumental studies by Hirschberg, Magnus, James, and others. The interest in the present little volume lies mainly in its assessment of the general lines of development.

ARNOLD SORSBY.

## SOCIAL ADJUSTMENT OF CHILDREN

*The Social Adjustment of Children. Manual to the Bristol Social Adjustment Guides.* By D. H. Stott, M.A., Ph.D. (Pp. 46. 25s.) London: University of London Press. 1958.

The main purpose of this book is to act as a manual to the *Bristol Social Adjustment Guides*,* which have been designed to assess and describe manifestations of emotional maladjustment and disorders of behaviour. They are essentially rating-scales of behaviour and do not provide developmental norms of social development. There are three such guides, designed for the assessment of children's behaviour in school, in residential care, and in family situations. Appropriate phrases in the guide are underlined by the user, who judges which of these phrases best describes the child's behaviour or attitudes in various situations. So far as

**The Bristol Social Adjustment Guides.* A Series of Diagnostic Forms and Templates. By D. H. Stott and E. C. Sykes. London: University of London Press. 1958.

possible the items are behaviourally orientated, and inference is reduced to a minimum.

For the purpose of scoring the items are arranged into groups or syndromes. These syndromes represent probably the weakest point of the scales, because they were arrived at by means of a kind of visual cluster analysis which is manifestly inferior to more orthodox procedures, although Dr. Stott, for some reasons which are not obvious, appears to consider it superior. The original data are not given, so that the reader cannot judge as to the adequacy of the analysis. In spite of this very serious shortcoming, which affects the method of scoring used for the guides, these may nevertheless be useful for research purposes in the hands of investigators who have sufficient statistical knowledge to use their own results for deriving proper scoring categories.

H. J. EYSENCK.

## BOOKS RECEIVED

*Review is not precluded by notice here of books recently received.*

***International Review of Neurobiology.*** Volume I. Edited by Carl C. Pfeiffer and John R. Smythies, with 14 Associate Editors. (Pp. 383+xii; illustrated. $10.) New York and London: Academic Press. 1959.

***Accouchement "Sans Douleur" au Point de Vue Psychiatrique.*** By Anne Melotte-Athmer. (Pp. 118.) Brussels, Turnhout: Brepols. 1959.

***Recent Advances in Public Health.*** By J. L. Burn, M.D., D.Hy., D.P.H. Second edition. (Pp. 370+xi; illustrated. 40s.) London: J. and A. Churchill, Ltd. 1959.

***Recent Advances in Surgery.*** Edited by Selwyn Taylor, D.M., M.Ch., F.R.C.S. Fifth edition. (Pp. 500+xiv; illustrated. 60s.) London: J. and A. Churchill, Ltd. 1959.

***The Student and Mental Health. An International View.*** Proceedings of the First International Conference on Student Mental Health, Princeton, N.J., September 5–15, 1956. Edited by Daniel H. Funkenstein, M.D., assisted by Stella B. Hanau, A.B., and George H. Wilkie, M.D. (Pp. 495+xxv. 35s.) London: H. K. Lewis and Co., Ltd., for the World Federation for Mental Health. 1959.

***Data for Biochemical Research.*** Edited by R. M. C. Dawson, Daphne C. Elliott, W. H. Elliott, and K. M. Jones. (Pp. 299+xiii. 63s.) London: Clarendon Press, Oxford University Press. 1959.

***The Diabetic Life: Its Control by Diet and Insulin and Oral Treatment by Sulphonyl-Ureas. A Concise Practical Manual.*** By R. D. Lawrence, M.A., M.D., F.R.C.P.(Lond.). Sixteenth edition. (Pp. 230+x; illustrated. 15s.) London: J. and A. Churchill, Ltd. 1960.

***Bibliography of Cancer Produced by Pure Chemical Compounds. A Survey of the Literature up to and Including 1947.*** By Otto Neubauer, M.D. (Pp. 604+xxvii. 42s.) London: Clarendon Press, Oxford University Press. 1959.

***The Central Nervous System and Behavior.*** Transactions of the Second Conference, February 22–25, 1959, Princeton, N.J. Edited by Mary A. B. Brazier, Ph.D. (Pp. 358; illustrated. $4.75.) New York: Josiah Macy Jr. Foundation. Washington, D.C.: National Science Foundation. 1959.

***Fluoridation. Errors and Omissions in Experimental Trials.*** By Philip R. N. Sutton, D.D.Sc.(Melb.), L.D.S.(Vic.). (Pp. 83+vii. 8s. 6d.) Melbourne: University of Melbourne Press. London: Cambridge University Press. 1959.

***British Surgical Practice. Surgical Progress 1959.*** General editors: Sir Ernest Rock Carling, LL.D., F.R.C.S., F.R.C.P., F.F.R., and Sir James Paterson Ross, K.C.V.O., LL.D., M.S., F.R.C.S., F.R.C.S.Ed., F.R.A.C.S., F.A.C.S., F.F.R. (Pp. 391+90+ix; illustrated. 52s. 6d.) London: Butterworth and Co. (Publishers) Ltd. 1959.

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## ROYAL COMMISSION'S REPORT

Three years' hard labour by the Royal Commission has produced a report[1] which will need careful study by the medical profession before its implications are fully grasped. By delaying the publication of this week's issue we have been able to give a fairly full summary of the Report in the Supplement. Any comment we may make is naturally that of a first reaction, a reaction that because of the timing of the publication must precede any considered appreciation by the British Medical Association as a whole, by the General Medical Services Committee and the Conference of Local Medical Committees, and by the Joint Consultants Committee and its constituent bodies. These various professional groups together constitute a somewhat elaborate machinery, but nevertheless faithfully represent the diversified nature of the medical profession, and a variety of interests within it which though not necessarily conflicting must eventually be harmonized if in the last analysis a broadly satisfied point of view is to be expressed. Certainly there is going to be no unison of approval of what the Royal Commission proposes.

If we may look first at the last part of the summary of the Commission's Report—on machinery—we may welcome the conclusion that the present machinery is suitable only for the disposal of minor matters. But just as there is no clear dividing line between minor surgery and major surgery, so the lines may still prove to be blurred when the Whitley machinery continues to attempt to grind out points of difference between Management and Staff Sides. The profession will still find that the approach to a problem by the trained bureaucratic mind will differ from that of the practising doctor who has to get on with a job in which empiricism is by and large a good and necessary guide. But on the recurring theme of the rate for the job the Commission's proposal to set up a Standing Review Committee on remuneration of doctors in the National Health Service is in principle to be welcomed. The first thing to be noted is that the Prime Minister is the person to be advised and not the Minister of Health. The Review Committee will not include a medical man. The profession will not be able to pass on its views direct to the Committee but only through the Government. The Commission thinks the Spens Reports do not provide a firm basis for professional remuneration. Professor John Jewkes, in his minority report, notes that for doctors the State is very largely a monopoly employer. His proposals for a review machinery are referred to below.

[1] *Royal Commission on Doctors' and Dentists' Remuneration, 1957-60*, Cmd. 939. H.M.S.O., London. Price 15s.

The Commission hopes that this new Review Committee will give weight to three factors: changes in the cost of living, changes in other professions, and the quality and quantity of recruitment in all professions. The Review Committee may make recommendations on its own initiative, on the Government's initiative, or on the profession's initiative through the Government. But the Prime Minister will decide whether or not to act on the the advice he gets. While we welcome the principle of building into the wage-structure of a permanent review-mechanism, it must be noted that there is a big shift of emphasis from the approach of the two Spens Committees. Looking at the problem of a profession about to be nationalized the Spens Reports emphasized—and rightly—"the normal financial expectations of general medical practice in the past, and to the desirability of maintaining in the future the proper social and economic status" of general medical practice and of consultant and specialist practice. The change of emphasis is important and needs to be looked at critically. The seven wise men of the Review Committee may decide that the profession of Medicine, in both quality and quantity, should at certain times be discouraged in relation to other professions. The State as paymaster may, through the power given to the Prime Minister, advised by the Review Committee, distribute its rewards and punishments to deflect the ambitious and able youth of any generation away from medicine into, say, electrical engineering. Here in fact is the danger that the State may become too powerful in its direction of the individual. As doctors the medical profession must always attempt to attract the best and to reward the best. It is not that it is self-seeking in a merely material sense. It must do all it can "to attract a suitable type of recruit." And it can say with assurance that unless it can do this, within the framework of collective responsibility in the community in which it lives, it cannot make its full and powerful contribution to the physical and mental well-being of its fellow-citizens. Medicine in Britain, if it is to continue to lead the world as it has done, and work out its own destiny in research and its application to the improvement of human well-being, must progressively become freer from the restrictions of State control. It is in this light that the proposals of the Royal Commission must be looked at.

The Royal Commission has had to consider the remuneration of dentists as well as of doctors in the N.H.S. It is not for us to comment on its recommendations about the payment of our colleagues in the dental profession. It must suffice to note that the Commission recommends that between the ages of 30 and 65 the average career earnings for doctors in the N.H.S. should be £102,000 and of general dental practitioners about £96,000. The Commission in fact recommends an average differential between the two, and one is driven to the conclusion that the extension of this by the Review Committee would end up in the State's guiding the differentials

between different professions according to the judgment of an all-wise directorate on the current requirements of professional expertness in the highly complex world in which we live. It may be that philosophers should be kings, and that the fate of professions should be governed in this way. But it all looks dangerously like the subordination of the individual to a hierarchy which ill suits a profession in which individualism, with all its faults, has been the mainspring of the healing art.

If we come down to detail there are certain divergences from the Spens recommendations which should be noted. For consultants and specialists the age at which remuneration was begun was 32, the Commission's age is 34. This may be a recognition of what is in fact happening. The Commission states that the broad relationship between the earnings of general practitioners and of consultants is unchanged. It depends on what one means by broad. Here is a comparison of the Pilkington scales with those in operation in 1954—that is, before the two interim awards of 1957 and 1959—with percentage betterment in parentheses.

| | 1954 | 1960 |
|---|---|---|
| | £ | £ |
| House Officers .. | 425- 525 | 675 (59%)- 750 (43%) |
| Senior Registrars .. | 1,100-1,400 | 1,500 (36%)-1,800 (29%) and after 4th yr. 2,100 (50%) |
| S.H.M.O.s .. .. | 1,575-2,025 | 2,000 (27%)-2,700 (33%) |
| Consultant (basic) | 2,100-3,100 | 2,550 (21%)-3,900 (26%) |

General practitioners will get an average of £450 more a year, but this includes £190 from interim increases. The increase is 22.8% over a recalculated 1955–6 level. Hospital staffs as a whole come off better than general practitioners, but this can be looked on as a readjustment of the consultant settlement of 1954. Yet Professor Jewkes, in his dissent, says that unless general practitioners' earnings are at least 30% above the 1955–6 level their real standard of living will have fallen over the past decade.

The Commission has recommended that for the period 1957–9 a sum of £11m. should be available for general practitioners and £9m. for hospital staff.

What provisional conclusions may one draw from all this? The profession will recognize first of all that the Royal Commission was given an extremely difficult task. Its members and its chairman, Sir Harry Pilkington, have impressed all with the thoroughness with which they collected and sifted evidence and the fairness with which they treated representatives of the profession who appeared before them. As to the recommendations, it is good that the young doctor has been especially singled out for favourable treatment. As merit awards have come to stay it is good, too, that at the other end of the professional ladder excellence and brilliance should have recognition in an A-plus award. But that the numbers of awards for consultants in the coming three years are to be fixed irrespective of the total number of consultants eligible cuts straight across the Spens recommendations. Presumably the Commission's decision is based on what it thinks the country can afford. But let us look at some of the "minor matters"—"limited weighting" and travelling expenses, are, it appears, allowed to those already enjoying them or on the verge of doing so. But not for those who come after. Here, it would seem, is a typical committee decision which will rankle, and from which Professor Jewkes dissents.

Inevitably in this quick and first survey we have had little opportunity to digest the argument in the report itself. But the immediate impression must be that the bright promise held out to the profession in 1946 and 1948 is becoming a little tarnished in the somewhat damp light of current economic embarrassments. But the profession did not ask to be nationalized. In the period between 1942 and 1948 it resisted the idea with some tenacity. It should still remain tenacious if it is to enlarge its area of freedom.

The Commission's recommendations of course fall below what would have been awarded on the basis of the Spens–Danckwerts formula. When the Government has considered the Commission's recommendations it will no doubt open negotiations with the profession. As important as discussions on detail will be agreement on the terms of reference of the Review Committee of seven and its composition. The profession will probably wish to see the terms of reference brought more into line with the Spens Committees' terms, because these emphasized the continuity of pattern and expectation within the profession itself. It was on this basis that nationalization was reluctantly accepted. The final formula is of the utmost importance.

The important minority report by Professor John Jewkes underlines some of the provisional observations made here—provisional because they are first impressions which may well be modified by the profession when it reaches its final conclusions. He recommends that the average net figure for general practitioners should be £2,550 and *not* £2,425. He considers that no change should be made in the *system* of distinction awards, but that the value of each should be increased by 30%. Domiciliary payments should also go up by 30%. and whole-time consultants should be paid for domiciliary visits. He is opposed to retrospective payments in any form. He agrees there should be new arrangements for reviewing remuneration—as indeed everyone does. But he considers the new machinery should take the form of an Advisory Council with wider functions than are proposed in the majority report. "The professions," he writes, "should have direct access to this Council, which might usefully include one or more eminent members of the medical profession. The Council should review remuneration every three years or sooner if the price level had changed either way by more than 10% from the time of the last settlement." Taking as an example to be followed the emergence and success of the University Grants Committee, Professor Jewkes hopes his proposed Advisory Council would evolve in the same way and become an organic part of the National Health Service. Many will agree with him.

## CARDIAC ARREST AND THE CENTRAL NERVOUS SYSTEM

Reports[1-5] of recovery from the neurological damage caused by cardiac arrest during operations have again raised the question of the critical period beyond which damage to the central nervous system is irreversible. The incidence of cardiac arrest (as distinct from deaths under anaesthesia from all causes) is not known, but from an analysis[6] of some American figures it can be estimated that about 300 deaths from cardiac arrest will occur each year in Great Britain, assuming the incidence in the two countries is the same. This would represent a total of 500 to 600 cases of arrest, with a mortality of about 50%. Cardiac arrest occurs most often in the first decade of life and is rather more common in males than in females[7]. Of the fatal cases, the great majority (87%) die within the first 24 hours, and long survival, with or without severe injury to the nervous system, is unusual.

Although changes in the nervous system will clearly depend upon the length of time during which there is no blood flow through the brain, there has often been confusion between cardiac arrest (absence of spontaneous heart beat) and circulatory arrest, which is the interval between onset of cardiac arrest and the initiation of effective cardiac massage. Thus a case of "resuscitation after 40 minutes of cardiac arrest"[8] received almost immediate cardiac massage through an already open chest, so that the duration of true circulatory arrest was, in fact, less than a minute. Further, cardiac arrest with ventricular fibrillation does not necessarily imply total circulatory arrest: a report[9] of complete recovery after 90 minutes of fibrillation (with no detectable pulse or blood pressure) can be explained only by the presence of a circulation adequate for cerebral requirements.

Neurological damage will be related in the first instance to the duration of true circulatory arrest. The upper limit for the period beyond which serious if not irreversible changes will occur in the nervous system is often said to be four minutes. However, the numerous cases of death after a circulatory arrest of less than four minutes emphasize the importance of other factors. In these fatal cases it has been shown that previous cardio-respiratory abnormalities—particularly hypotension, cyanosis, and arrhythmias—were usually present. Clearly then the "four-minute limit" cannot be applied in the presence of pre-existing cerebral hypoxia (from any cause), and for this reason no fixed time limit should be given suggesting there is the same margin of safety for all cases. This view is endorsed by a study of fatalities. Thus in one case[10] circulatory arrest of two minutes was followed by a state of tetraplegia and coma, with death two and a half months later. In another,[11] the period of arrest was only one minute, yet the result of this was that the patient remained in a decorticate state for six and a half months. In both these cases there was evidence of cardio-respiratory distress before the onset of cardiac arrest. On the other hand, the opposite, but extremely rare, situation is represented by a report[12] of complete recovery after six minutes of true circulatory arrest. Obviously resuscitatory measures must always be maintained in the hope of a favourable outcome whatever the duration of the circulatory arrest.

The mechanism by which damage to the central nervous system is brought about is complex. Not only is oxygen no longer delivered to the brain but there is a lack of all other metabolic requirements as well as an accumulation of waste products, including carbon dioxide. The immediate treatment is by cardiac massage and artificial respiration with pure oxygen. In the human brain the effects of circulatory arrest are remarkably variable (in contrast to those seen in the experimental animal). The neurological sequelae range from slight impairment of intellect, memory, or vision, to epilepsy, dementia, decerebrate rigidity, and death. Clinically the minor abnormalities may be the more important in the apparently recovered case in that they are most easily overlooked. A slight impairment of intellect or memory or a minor personality change may first be noted by the patient's relatives or employer rather than by his physician. In fatal cases the neuropathological picture also varies from relatively slight cell loss in the cerebral cortex, hippocampus, and cerebellum up to gross devastation of these structures and of basal ganglia and white matter.

A further important effect of arrest of blood flow to the brain is vasodilatation and engorgement of the vascular bed. The delayed cerebral oedema which this causes—developing in the course of days rather than hours—may lead to further damage to nervous tissue. For this reason the intravenous administration of hypertonic fluids (50% glucose, human serum albumin, or urea in fructose) forms an important part of the management of cases of cardiac arrest. Another delayed complication is hyperthermia, which may also require treatment.


[1] Burnett, W., and Smith, A. N., *Brit. med. J.*, 1959, **2**, 241.
[2] Clemetson, C. A. B., ibid., 1959, **2**, 14.
[3] Blair, D. W., Irvine, W. T., and Taylor, R. C., ibid., 1958, **1**, 1521.
[4] Walton, R. S., ibid., 1960, **1**, 155.
[5] Fleming, W. B., *et al.*, ibid., 1960, **1**, 157.
[6] Milstein, B. B., *Ann. roy. Coll. Surg. Engl.*, 1956, **19**, 69.
[7] Keating, V., *Anaesthetic Accidents*, p. 261, 1956, London.
[8] Touroff, A. S. W., and Adelman, M. H., *J. Amer. med. Ass.*, 1949, **139**, 844.
[9] Schlachman, M., Sorbello, N., and Haddad, S., *Arch. intern. Med.*, 1958, **101**, 650.
[10] Biemond, A., *Folia psychiat. neerl.*, 1958, **61**, 540.
[11] Meyer, A., *Proc. roy. Soc. Med.*, 1956, **49**, 619.
[12] Wolff, W. I., *J. Amer. med. Ass.*, 1950, **144**, 738.

The literature of cardiac arrest is inevitably weighted by dramatic accounts of cases in which the period of arrest was unusually long and the reversible symptoms severe. Such exceptional cases cannot justify complacency on the part of anaesthetist or surgeon. The initiation of effective cardiac massage with the minimum of delay remains the essence of successful treatment: its execution is feasible in the great majority of cases, including those occurring in out-patient and casualty departments. Even in the wards a knife should be quickly obtainable, and mouth-to-mouth respiration can be carried out while a Boyle's apparatus is being fetched.

## CHOICE OF A PENICILLIN

A recent annotation[1] in this journal criticized the launching of a new penicillin by way of a public press conference without any previous publication about its properties in medical journals. The profession is still very incompletely informed about this antibiotic ("broxil"), but a paper by E. T. Knudsen and G. N. Rolinson[2] has outlined the basis for the claim that it produces higher blood levels than other oral penicillins, and we publish in this issue (p. 527) one by Professor L. P. Garrod containing new information about its antibacterial activity. Comparison was made with penicillins G and V, and in a test so devised as to take account of resistance to penicillinase it is shown that the new penicillin is much more active than penicillin G against penicillinase-forming staphylococci, a superior activity shared to some extent by penicillin V. Evidently "broxil" may prove to be of great value in treating penicillin-resistant staphylococcal infections, although clinical confirmation of this superiority may be deemed desirable. Such other organisms as have been tested so far are less sensitive to broxil than to penicillin G—streptococci and pneumococci by only a small margin, which may be of little significance when higher blood levels can be attained, but by a very substantial margin in two other organisms, *H. influenzae* and *Proteus*. The relative weakness of broxil against these is shared to some extent by penicillin V.

These observations appear to call for some re-thinking and for a good deal of further work. Penicillin V was discovered and first used in Austria, and interest centred almost wholly on its acid resistance and consequently more regular absorption. A few workers found minor differences in its activity compared with penicillin G, but these have been ignored and the two have been regarded as equivalent. It now appears that they are by no means equivalent: penicillin V is more active against many resistant staphylococci—a property in which broxil excels still further—and much less so against *H. influenzae*, the principal pathogen in chronic bronchitis, and *Proteus*, a common cause of urinary-tract infections. This property in penicillin V may have contributed to the finding of J. I. Burn *et al.*[3] that penicillin-resistant staphylococcal infections responded as well to treatment as sensitive ones. The resistance of *H. influenzae* to penicillin V will reinforce the belief of the British Tuberculosis Association[4] that preventive treatment with this antibiotic in chronic bronchitis achieved its success not by interfering with the activities of this organism but more probably with those of the pneumococcus.

There may be differences in the activity of these penicillins against other organisms which have yet to be revealed, whether to the advantage of those more recently introduced or the reverse. A systematic exploration of this field seems overdue, but in the meantime, and in connexion with those infections about which information is here made available, it has to be decided whether tests of bacterial sensitivity performed only with penicillin G can henceforth be considered adequate as a guide to treatment. No one wants to burden the clinical laboratory any further, but there can evidently be circumstances in which this commonly performed test could be more useful if it were somewhat elaborated.

[1] *Brit. med. J.*, 1959, **2**, 940.
[2] Knudsen, E. T., and Rolinson, G. N., *Lancet*, 1959, **2**, 1105.
[3] Burn, J. I., *et al.*, *Brit. med. J.*, 1957, **2**, 193.
[4] British Tuberculosis Association, ibid., 1960, **1**, 297.

## STEROIDS AND STEATORRHOEA

Though cortisone and its analogues produce such dramatic effects in a wide variety of disorders, it is still fair to say that, despite intense study of them, the mechanism by which these effects are produced is ill understood. As a result empirical experience rather than theory must be our guide in the treatment of disease with corticosteroids. Theory or hypothesis later endeavours to explain the empirical experience and more often than not fails in its efforts. It is clear, for example, that a good clinical response to cortisone does not necessarily imply a deficiency of adrenal function judged by normal criteria. Production of cortisol seems to be normal in most cases of rheumatoid arthritis or of ulcerative colitis, though in both conditions a rise in production to abnormally high levels provoked by corticotrophin may produce great clinical benefit.

Among the many conditions which sometimes benefit from steroid therapy is steatorrhoea, but in this case the similarity to hypoadrenalism is closer because other features in common with Addison's disease are frequently present. Thus there is often asthenia, pigmentation, disturbance of water excretion, low blood pressure, and even low serum sodium. To these features is commonly added a low, often very low, excretion of 17-ketosteroids. This combination of features is not found only in steatorrhoea; it occurs in many states of malnutrition. When it is due to advanced malignant disease or to advancing tubercle the suspicion may be strong that severe hypoadrenalism is caused by direct involvement of the gland in the disease process. Yet the cortisol in such patients may be at a normal level in the plasma and excreted in normal amounts in the urine.

[1] Wollaeger, E. E., and Scribner, B. H., *Gastroenterology*, 1951, **19**, 224.
[2] Taylor, W. H., *Clin. Sci.*, 1954, **13**, 239.
[3] Flear, C. T. G., Cooke, W. T., and Quinton, A., ibid., 1959, **18**, 137.

Likewise it is necessary to be guarded about attributing any of the symptoms or signs in steatorrhoea to hypoadrenalism. Malnutrition from many causes may impair adrenal and even anterior pituitary reactivity, and Dr. J. N. Mickerson, who discusses some cases at p. 529 of the journal this week, is no doubt correct in claiming that such sluggishness occurs in steatorrhoea. But impairment of water diuresis is an unreliable test to use for adrenal function in this disease because of the impairment of water absorption.[1-3] Mickerson found in one case when the water load was given intravenously that renal elimination of water was prompt and complete. This does not support the concept of a clinically significant degree of hypoadrenalism. Mickerson also suggests that many patients with steatorrhoea fail to seek advice until a state of pituitary exhaustion supervenes. Such a state of exhaustion is a hypothetical concept at present, unsupported by experimental evidence. The metabolic disturbances in steatorrhoea are very complex, and derangement of adrenal function may well play a small part in the development of these disturbances. But the role of this factor should not be overemphasized. It will not explain the greater part of the clinical picture, any more than will a deficiency of folic acid. Many other factors are involved, and it is still necessary to retain a broad view of the complex interplay of these various influences.

## DIAPHRAGMATIC HERNIA IN INFANCY

Apart from rare traumatic cases diaphragmatic hernia in infancy is probably always congenital. The term, however, comprises several conditions which are so different anatomically and clinically as to constitute different diseases.

The most common in Great Britain is hernia through the oesophageal hiatus of a small portion of the stomach; this is usually termed a hiatus hernia or partial thoracic stomach. The cardia is usually within the thoracic cavity, though it is debatable whether the primary anomaly is an unduly large hiatus which allows a portion of the stomach to slide upwards into the thorax or whether it is a developmental shortening of the oesophagus. In the less common para-oesophageal hernia the oesophagus is not shortened and the cardia is in its normal intra-abdominal position, but a pouch of stomach enters the thorax alongside the oesophagus through an enlarged diaphragmatic opening. Hiatus hernia has been well reviewed by several British workers.[1-3] The main symptom is vomiting, which often starts in the first weeks of life and is not infrequently projectile in nature. The vomitus contains much mucus and often contains altered blood. Parents may not correctly interpret the nature of the brown vomit unless specifically questioned on this point. Vomiting is usually severe enough to interfere with growth and it is not much influenced by antispasmodics. In older children bleeding from the oesophagitis may result in severe anaemia. In a minority of cases dysphagia, which develops insidiously, is the ominous symptom pointing to the formation of oesophageal stricture, a most serious complication. Diagnosis can be confirmed only by radiographic screening with barium. This is a highly specialized technique, to be attempted only by an experienced paediatric radiologist.

Treatment should be medical in the first instance, because symptomatic recovery is usually spontaneous by the age of 2 years. In some patients the disappearance of symptoms is concomitant with disappearance of the hiatus hernia, but this is not invariable. The infant is kept upright day and night, either by the use of a chair specially constructed for the purpose or by suspending him in a special harness. Feeds should be thickened with cereal, and solid feeding should be introduced as soon as possible. An alkali with each feed may reduce the tendency of the acid reflux from the stomach to produce oesophagitis. The indications for surgical treatment are a matter of considerable controversy. Clear indications for operation are persistent oesophagitis or formation of stricture in spite of medical treatment.

A completely different picture unfolds when the hernia takes place through a large hole in the postero-lateral muscular segment of the diaphragm, the foramen of Bochdalek so beloved of examiners. Though the infant with this type of diaphragmatic hernia may be free of symptoms, in over 90% severe symptoms arise soon after birth. They are usually respiratory difficulty with severe attacks of cyanosis. Aspiration of vomitus may aggravate the trouble. Inspection often reveals diminished movement of the affected side, usually the left. The percussion note may be dull or tympanitic. The breath sounds are diminished, and intestinal gurgling sounds may be audible within the thorax. Diagnosis can be confirmed by postero-anterior and lateral *x*-ray films. These will show absence of the diaphragm, multiple radiotranslucencies representing loops of intestine within the thorax, mediastinal shift to the opposite side with compression atelectasis on the affected side, and often a relative absence of gas within the abdomen.[4-6] The prognosis of herniation through the foramen of Bochdalek in young infants without treatment is very poor. On the other hand, immediate surgical repair, most often by the abdominal route, carries a small mortality in experienced hands and should be advised without delay. The results are excellent and recurrence is virtually unknown.

In a third group, the hernia occurs through the foramen of Morgagni, a defect in the anteromedial tendinous portion of the diaphragm just posterior to the sternum. This is a rare defect in which symptoms depend for their severity on the volume of abdominal contents which have entered the thorax. Frequently, the history in infancy is of repeated respiratory infections. The true nature of the unusual *x*-ray appearances is revealed by barium swallow. Surgical repair should be advised without delay.

[1] Carré, I. J., Astley, R., and Smellie, J. M., *Lancet*, 1952, **2**, 1150.
[2] Smellie, J. M., *Proc. roy. Soc. Med.*, 1954, **47**, 531.
[3] Burke, J. B., *Brit. med. J.*, 1959, **2**, 787.
[4] Gross, R. E., *Amer. J. Dis. Child.*, 1946, **71**, 579.
[5] Swenson, O., *Pediatric Surgery*, 1958, New York.
[6] Reed, J. O., and Lang, E. F., *Amer. J. Roentgenol.*, 1959, **82**, 437.

*Drug Treatment of Disease*

# ACUTE AND CHRONIC GLOMERULAR NEPHRITIS

BY

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## ACUTE GLOMERULAR NEPHRITIS

There is no known way to prevent acute glomerular nephritis from developing into chronic glomerular nephritis, though at one time antihistamine and nitrogen mustard derivatives were given for this purpose. The aim of treatment is to prevent the patient dying from the three immediate complications of the disease—namely, acute renal failure, heart failure, and hypertensive encephalopathy.

It is customary to keep the patient in bed, and in most cases this induces a brisk diuresis within 24–48 hours. A course of penicillin, 250 mg. twice a day by intramuscular injection for 3–5 days, is begun after swabs from the throat or any obviously infected area have been taken. For the first day no food is given and the intake of fluid is limited to 500 ml. At the end of this time it is usually clear which direction the illness is taking. If the 24-hour urine volume is greater than 1,000 ml., no further dietary or fluid restrictions are necessary; if it is between 500 and 1,000 ml. the intake of fluid is increased by an amount equal to that of the urine excreted, and a low-salt and low-protein diet is given; if the urine volume is below 500 ml. the patient is considered to have acute renal failure. This is not the place to discuss the treatment of that emergency.

Most patients with acute nephritis have heart failure, but this rarely needs special attention. Occasionally acute attacks of left heart failure make it necessary to give digitalis—digoxin ¼ to 1 mg. intravenously, followed by 0.25 mg. six-hourly. If there is bradycardia before the administration of digitalis it may be difficult to gauge the dose.

Hypertensive encephalopathy will usually respond to intravenous injection of sodium amylobarbitone, 0.3 to 1 g., followed by 0.4 to 0.6 g. six-hourly. Alternatively, sodium thiopentone, 0.1 to 0.5 g., can be used for the initial injection. Hypotensive drugs are also useful, though the patient needs greater supervision; in an emergency, however, 25 mg. of hexamethonium bromide intravenously may be life-saving.

The administration of adrenal steroids and mercurials in acute nephritis is contraindicated. Steroids may precipitate heart failure, aggravate the rise in blood pressure, and delay the onset of the diuresis; they are also ineffective in the treatment of acute renal failure when it is a complication of acute nephritis. Mercurials rarely increase the flow of urine, and the attempt to obtain a diuresis in this way in acute nephritis has little to justify it. After the initial course of penicillin, treatment is continued with phenoxymethylpenicillin (penicillin V), 125 mg. daily by mouth until the proteinuria has ceased.

## CHRONIC GLOMERULAR NEPHRITIS

The cause of chronic glomerular nephritis is unknown, but it is a reasonable precaution to put the patient on daily oral penicillin V in the hope that acute exacerbations after infections with haemolytic streptococci may be avoided. The dose should be 125 mg. once a day indefinitely. But destruction of the renal parenchyma usually proceeds more or less rapidly. As renal function diminishes it is often possible to prevent those acute deteriorations in function which accompany sudden changes in electrolyte and water balance (diarrhoea and vomiting) or blood volume (acute haemorrhage), or which are associated with renal infection. The treatment of acute disturbances of electrolytes, acute haemorrhage, and superimposed renal infections in chronic glomerular nephritis are not discussed here. The following symptoms and complications can sometimes be relieved by drugs.

### Gastro-intestinal Symptoms

The patient with anorexia can be helped by frequent small meals, and, when there is an unpleasant ammoniacal halitosis, by frequent mouth washes. The most important advance in the relief of misery in the end stages of chronic renal failure has been the use of chlorpromazine ("largactil") 25–100 mg. by mouth to relieve vomiting. More recently perphenazine ("fentazin"), 2–4 mg. by mouth, has been used with equal success; it is less stupefying than chlorpromazine and is sometimes better for those patients who can still get about. Chlorpromazine may occasionally cause acute hypotension, but with the small intermittent amounts which are given the other complications, such as jaundice and neurological signs, are unusual. It is most useful in helping to relieve apprehension and in reinforcing the effect of other sedative or analgesic drugs.

It is important to avoid treating the constipation of chronic renal failure with magnesium sulphate, for it may cause magnesium intoxication.

### Anaemia

The anaemia of chronic renal failure is due principally to depressed erythropoiesis. In advanced cases there may also be haemolysis and occasionally there is iron deficiency from a slow gastro-intestinal haemorrhage or from menorrhagia. Before treating the anaemia it is important to remember that patients with renal failure are often unaffected by moderately severe anaemia. It is therefore unnecessary in many instances to try to treat the anaemia unless the haemoglobin falls below approximately 70%, when it may precipitate cardiac failure. It should also be remembered that in chronic renal failure a rapid rise in the haematocrit (packed cell volume) after a transfusion may cause a sudden deterioration in renal function.

Depressed erythropoiesis can be corrected by transfusion of packed cells or treated with the administration of cobaltous chloride.

Packed red cells are given in small amounts, 100–200 ml. at intervals of two to three days, during which creatinine clearances and the blood urea are

measured. The total number of transfusions needed is determined by their effect on renal function and the haemoglobin concentration. Cobaltous chloride, 100 mg. by mouth or by intramuscular injection, three times a day, has been given with some success, but its side-effects severely limit its use. It has little effect on erythropoiesis unless treatment is continued for over a month, and in the interval there may be vomiting, paraesthesiae, and nerve deafness.

Haemolysis will sometimes respond to the administration of steroids—cortisone 50–100 mg., prednisone 10–20 mg., or triamcinolone 2–4 mg. Iron deficiency is best treated with intramuscular injection of iron (" imferon ").

### Calcium Deficiency

In prolonged chronic renal failure the intestinal absorption of calcium is diminished, and this may lead to osteomalacia in adults and rickets in children. The bone changes can be reversed by giving large doses of calciferol, 1–3 mg. per day. The dose must be carefully adjusted for each patient. Sometimes even greater quantities of calciferol are needed, but it is essential to estimate the plasma calcium at regular intervals and to be alert for symptoms of hypercalcaemia—namely, polyuria, thirst, and weakness.

### Hypertension

In chronic renal failure a rapidly rising blood pressure is often the beginning of the end. There is some evidence, however, that if the blood pressure is controlled the deterioration of renal function which usually follows such a rise may be prevented. An attempt to lower the blood pressure must be made when there is malignant hypertension, and it may sometimes be useful in the treatment of hypertensive cardiac failure.

The success of treatment will depend to a great extent on the response of the renal vasculature to the fall in pressure. If there is an accompanying vasodilatation, renal function either will remain unchanged or may improve. If the pressure falls but there is no vasodilatation, renal function will deteriorate. As a rough guide, the dividing line between these two responses seems to be when the blood urea is around 70 to 100 mg. per 100 ml. If the blood urea is greater than this, a fall in blood pressure may cause the renal failure to become worse, and treatment will have to be discontinued. The hypotensive drugs which are least likely to produce this effect are those that lower the pressure gradually. These are reserpine, 0.25–1 mg. daily by mouth, hydrallazine, 50–200 mg. daily by mouth, and occasionally chlorpromazine, 25–100 mg. daily by mouth. If these substances do not lower the blood pressure, mecamylamine, 5–30 mg. daily by mouth, or pentolinium tartrate, 6–30 mg. daily subcutaneously or intramuscularly, are also given. Occasionally phentolamine, 50–100 mg. by mouth, will lower the blood pressure in chronic renal failure in the absence of a phaeochromocytoma.

### Hiccup

The inhalation of carbon dioxide and the administration of various antihistamine derivatives continue to be the only treatment of any value for hiccups. Suitable drugs are perphenazine, 2–8 mg. per day by mouth ; chlorpromazine, 25–200 mg. per day by mouth ; and mepyramine, 100 mg. four-hourly. In intractable cases phrenic crush may be effective.

### Central Nervous System

The treatment of hypertensive encephalopathy has been mentioned earlier. At first sleeplessness can be treated with chloral 0.5 g. at night. Later, barbiturates such as sodium amylobarbitone 0.2 to 0.6 g. may be needed. Terminally, sleeplessness, restlessness, and dyspnoea may respond only to large amounts of paraldehyde, 4–8 ml. by intramuscular injection. Sometimes it may be necessary to combine the administration of paraldehyde with that of morphine, chlorpromazine, and a barbiturate before the patient obtains any rest. In some terminal cases the tolerance to opiates and barbiturates is remarkable and is difficult to explain.

Muscular twitches usually appear only in the terminal stages and do not need to be treated specifically unless they cause the patient some distress. They can be subdued temporarily with the intravenous administration of 10% calcium gluconate 10 ml.

### Retention of Waste Products and Acidosis

At the present time it is not the custom to try to control the level of blood urea by restriction of protein unless the blood urea is rising rapidly or is greater than about 100 mg. per 100 ml. A temporary reduction in blood urea can be achieved by the use of anabolic steroids, either norethandrolone (" nilevar "), 50 mg. per day by mouth, or norandrostenolone phenylpropionate (" durabolin "), 25 mg. intramuscularly twice a week.

It is also debatable whether the acidosis of chronic glomerular nephritis should be treated. It depends on whether the patient feels any better after treatment. Sodium bicarbonate, 3–9 g. per day, or sodium citate, 15–30 g. per day, may produce a temporary improvement in general well-being and appetite and diminish headache. Occasionally, however, the patient feels worse, and he may develop cardiac failure. Sodium lactate (1/6 molar) is sometimes given intravenously. Again the result obtained should decide whether to repeat the treatment. Some patients with long-standing acidosis are made acutely ill, and may develop severe vomiting and confusion.

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" A problem which faces all Management Committees is that of the storage of medical records. An idea of the magnitude of the task locally [in the Portsmouth Group] can be gathered by the fact that each year there are something like 30,000 admissions and 100,000 new out-patients and casualty records. In 1954 an experiment was undertaken at Saint Mary's Hospital to see if micro-filming would provide a practical answer to the problem. It was found, however, that the photographing of the records would take approximately seven months, and, including the additional indices necessary, would cost something in the nature of £300 per annum. Over a period of, say, seven years this would amount to £2,000, whereas suitable racking to cover the same period could be provided for about £400. Provided, therefore, that there is physical room, economically the storage of original records is much the better proposition. Additionally it is preferable, since medical staff prefer original notes and it is speedier to produce them rather than reproduce from a microfilm in the event of the readmission of a patient. As space was available in Portsmouth it was decided to proceed with racking and abandon the microfilm experiment." (*Report for the Period July 1948 to December 1958*, Portsmouth Group Hospital Management Committee.)

# Correspondence

*Because of heavy pressure on our space, correspondents are asked to keep their letters short.*

## World Refugee Year

SIR,—I have no doubt that members of our profession are aware of the appeal which is being made throughout the world this year for help for refugees, but there is one feature of this great effort which is of particular concern to us, and in respect of which the United Kingdom Committee for World Refugee Year has approached the Association for help.

The work of the International Refugee Organizations since the war has inevitably led to the "creaming off" of the population of refugee camps. Those who are left are mainly the old and handicapped, sometimes loosely described as "difficult cases." Included in this group is a smaller number of refugees who need special psychiatric treatment and advice to help them become normal members of society again. A mental health expert from the World Federation for Mental Health has now begun the work of visiting refugee camps in Europe to organize counselling or therapeutic teams as the need may require, and the United Kingdom Committee has undertaken to provide £5,000, which, it is estimated, will cover the expenses of the first year's work.

At a recent meeting the Council decided to send a donation of 100 guineas towards this particular project, and it asked me to appeal to all members of the Association for additional support. I feel sure that members of the profession would like to be associated with this very necessary project, and I shall be most grateful if you would give this appeal your sympathetic consideration. Donations should be sent direct to the United Kingdom Committee for World Refugee Year, 9, Grosvenor Crescent, London, S.W.1, earmarked for this specific medical project.—I am, etc.,

SOLOMON WAND,
Chairman of Council,
British Medical Association.

B.M.A. House,
London, W.C.1.

## Hospital Infection and Visitors

SIR,—A great deal of attention has been devoted to wound infection in hospitals during the last few years, and a great deal of painstaking work, tracing the numerous sources of infection and the mode of spread, has been carried out. Attention has been focused principally on resistant strains of staphylococci, how they arise, where they are to be found, and how to eliminate them. It has been clearly demonstrated that staphylococci colonize in the vestibule of the nose and are transferred by the patients' fingers to other areas of skin, to blankets, dressings, etc., and to every nook and cranny by dust.

Methods of elimination involve searching for carriers, barrier nursing, frequent washing of blankets or even their destruction, evacuating wards for thorough cleansing and repainting, in addition to overhauling and tightening up aseptic techniques in both medical and nursing staff. What is the good, however, of expending so much time and labour trying to eliminate infection unless more precautions are taken to prevent reinfection?

At least four times a week, and in some hospitals more frequently, the wards are invaded by hordes of visitors coughing, sneezing, some doubtless with boils and blains, and probably some with open tuberculosis. After an orgy of hugging, kissing, nose-scratching, and pawing of patients and blankets they disappear leaving the wards in a state comparable to a down-town saloon. This invasion of visitors must surely nullify all attempts to prevent reinfection. With the increasing menace of antibiotic-resistant organisms it seems to me that steps must be taken to eliminate this obvious loophole if serious outbreaks of infection are to be avoided.—I am, etc.,

Department of Surgery,
University of Manchester. A. M. BOYD.

## Retinal Burns after Sun's Eclipse

SIR,—I should like to thank the surgeons of the Sussex Eye Hospital for drawing attention to the danger of looking directly at the sun (*Journal*, December 26, p. 1487). As a result of my wartime work on this subject for the Royal Australian Navy[1] and my research with Sir John Eccles, F.R.S., on rabbits[2] it became obvious that there was no filter generally available to the public through which it was safe to view the sun directly. Therefore, for years I have advocated the use of a perfectly safe indirect, or projection, method of watching an eclipse.[3,4] This is based on the principle of the pinhole camera. The sun's image is projected on a white surface, and the observer, with his back to the sun, watches the projected image. The following details have proved very satisfactory. Make a hole with a pencil, about 0.3 in. (7.5 mm.) in diameter, in the centre of a piece of cardboard about one foot (30 cm.) square and hold or arrange it at such an inclination that the sun strikes it at right angles and shines through the hole on to a white surface, placed at the same inclination at a distance of about 10 ft. (3 m.). The image is about one inch (2.5 cm.) in diameter. The Ophthalmological Society of Australia (B.M.A.) has approved this method and has recommended that the public health and educational authorities should instruct the public in its use.

Finally, regarding the unilaterality of the cases reported from the Sussex Eye Hospital, my surveys of 250 cases following two eclipses in Australia[3,4] showed that in 74% of cases only one eye was affected (right eye 47%, left eye 27%).—I am, etc.,

Sydney, Australia. JAMES A. F. FLYNN.

REFERENCES

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2 Eccles, J. C., and Flynn, J. A. F., ibid., 1944, **1**, 399.
3 Flynn, J. A. F., *Trans. ophthal. Soc. Aust.*, 1952, **12**, 7.
4 ——: *Med. J. Aust.*, 1960, **1**, 85.

## Breast or Bottle?

SIR,—In your issue of January 16 (p. 195) Dr. V. M. Crosse, with her vast experience in the care of premature babies, strongly disagrees with the statement in our report,[1] that human milk is an inadequate food for small premature babies in the early weeks of life. Secondly, if we understand her aright, she thinks that we claim that our artificially fed premature babies gained more rapidly than normal. Actually we considered their rate of growth to be approximately normal. At 41 weeks from the beginning of gestation, the mean weight of each birth weight group of the prematurely born was about 7 lb. (3.175 kg.) or very near the mean weight of babies remaining in the uterus until term. Most of these premature babies were partly or wholly artificially fed after the first one or two weeks of life. Moreover,

we were pleased to find that in the subsequent months (i.e., after 41 weeks from conception), their mean weights approximated to those of full-term infants of the same age—if age is reckoned from the beginning of gestation. We therefore claimed that a processed dried milk, as given, allowed of normal growth in premature infants.

On the other hand, our premature infants of low birth-weight fed on human milk with no cow's milk supplement in their early weeks, had smaller weight gains than those artificially fed, and we therefore concluded that their gains were inadequate. We agree with Dr. Crosse that the number fed wholly on human milk who remained in hospital after four weeks of age was small, but nevertheless, however the feeding groups are subdivided, those fed on human milk only have the lower gains in weight (see our Table 39). We are not alone in finding that gains in weight are inferior on human milk. Table 37 in our report quotes figures derived from other publications, including a paper by Dr. Crosse herself, showing the percentage by which the gains of small premature babies given processed cow's milk exceeded the gains of similar premature babies given human milk, as follows: Crosse *et al.*[2] 23% ; Gordon *et al.*[3] 26% ; Kagan *et al.*[4] 31% ; our own series 30% ; and Rothe-Meyer[5] 25%. So perhaps our statement on the inadequacy of breast milk for premature infants was not as startling as Dr. Crosse suggests. Moreover, calculation of the normal increment to the body of the foetus *in utero* during the latter part of gestation demonstrates that a diet of human milk cannot provide enough protein for such an increment, and hence will not permit of normal growth of small premature infants (Young *et al.*[6]). Infants receiving human milk alone would receive a maximum of about 1.4 g. protein per lb. (0.45 kg.) body weight—even if we assume a calorie intake as high as 70 per lb.—and we believe there is no reasonable doubt that this protein intake is inadequate for the small premature infant in his early weeks (see Tables 42, 43, and 44 in our report).

Dr. Crosse states that human milk is the food best tolerated by premature infants. In our series human milk was always given for the first week of life because we, too, had the impression that at this early stage it was better tolerated. However, we had no factual data to establish this. Perhaps Dr. Crosse has published such data, and, if so, we are sorry we have overlooked the article. After the first one or two weeks of life, however, we used dried milk feeds with confidence, and the good progress of our artificially fed premature babies prove that the feeds were excellently tolerated.

Relatively few premature infants of low birth weight manage to establish themselves on the breast. In our report (p. 41) we tried to set out fairly some practical points which may help in deciding whether or not to augment with a dried milk supplement the protein intake of such an infant. We have nowhere advocated that "the use of human milk for premature babies should be discontinued." So we hope that Dr. Crosse's fears about the possible ill-effect of our report on the choice of food for premature babies may prove groundless.

Dr. J. H. Patterson, whose letter also appeared in the *Journal* of January 16 (p. 196), refers to the feeding of full-term infants, but perhaps he has not read our report. In it we state that "since we are fully aware that the emotional link between mother and child is of the utmost importance to the child, conclusions drawn from this investigation must not be taken to detract in any way from the importance of this aspect of breast-feeding."—We are, etc.,

B. LEVIN.
HELEN M. M. MACKAY.
V. G. OBERHOLZER.

Queen Elizabeth Hospital for Children,
London, E.2.

REFERENCES

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6 Young, W. F., Poyner-Watt, P., Humphreys, H. C., Finch, E., and Broadbent, I., *Arch. Dis. Childh.*, 1950, **25**, 31.

SIR,—I was interested to read the recent letters concerning your leading article "Breast or Bottle?" (*Journal*, December 5, p. 1239). I was educated to the belief that breast-feeding was far superior to bottle-feeding. However, six years of general practice have greatly modified my views. I can, in fact, think of no baby in my practice that has fared worse on correct bottle-feeding than on the breast. I know of many that have thrived on a bottle after being dissatisfied with the breast. I believe that breast-feeding is ideal when both baby and mother are happy with it. I am also sure that a contented mother is as important as a contented baby, and that in view of the excellence of modern artificial feeding there should be no hesitation in placing the baby on the bottle when discontentment with breast-feeding by either mother or child cannot easily be corrected.

A great advantage of bottle-feeding, on which little stress seems to be placed by authorities on infant-feeding, is that the mother can have an occasional break from the baby-feeding routine. This is a great morale raiser, and I consider it enhances rather than lessens maternal affection. It also gets the baby used to being looked after by others from time to time from an early age. Arguments for breast-feeding based on the fact that it is "Nature's way" seem to be flimsy. Civilized man's entire existence is unnatural, and most of medicine is devoted to correcting Nature's mistakes, failures, and omissions.—I am, etc.,

H. A. D. SHIRLAW.

Upholland,
near Wigan.

## Congenital Abnormalities

SIR,—The contention of Dr. M. J. Pleydell (*Journal*, January 30, p. 309) that congenital abnormalities occur more frequently in urban than in rural populations, and may have an infective basis, is supported by the following experience. In 1938 one of the three district midwives in Beverley (Yorks) delivered six babies with spina bifida in 10 days. She had encountered no cases in her previous four years' working in the compact little town.—I am, etc.,

K. D. SALZMANN.

Reading.

## Congenital Dislocation of the Hip

SIR,—As a surgeon who has benefited greatly from Dr. R. A. Strang's work on the early diagnosis of congenital dislocation of the hip I should like to congratulate him on his too brief summary of it (*Journal*, January 23, p. 279). I hope that before long he will give a full account of his methods, the different conditions he has found, and the help and the obstructions he has met from colleagues. But there is something very wrong in the situation he describes, though he does not labour this point. C.D.H. can be diagnosed at birth ; I have very recently seen a case detected at 20 minutes of

age; the previous record in my experience was 16 hours. Yet the average age at which I see these cases is about 20 months; I have also recently seen a case diagnosed at four and a half years, after some two years of limping.

Where does the responsibility lie? If our profession were run as an efficient business with the object of diminishing suffering, every baby would be examined for orthopaedic defects very soon after birth. The obstetrician does not regard this as his duty, and it is obviously impossible to bring in an orthopaedic surgeon in every case. Surely those who should understand and apply the simple investigations needed are the general practitioners, the clinic doctors, and the paediatricians. Dr. Strang records the examination of 4,500 children under a year old; others have seen equal or greater numbers, but how many of them have approached his record in avoiding crippling?

The single point that should cause suspicion of a hip joint in a baby is limitation of abduction. There is no difficulty in learning the normal range of this movement, and if this is diminished the baby should immediately be sent for investigation and treatment. Here a difficulty arises the extent of which is very difficult to determine, but I have had complaints from many mothers that on taking a new-born baby with a dislocated hip to orthopaedic clinics they were told to report back, usually in six months, "for reconsideration." If anyone doubts this widespread reluctance to treat certain conditions of the very young, let him consider that in most orthopaedic clinics treatment of babies with congenital scoliosis is refused completely. The reason for this is apparently that some recover spontaneously; though on the other hand some progress to the dreadful crippling of "idiopathic scoliosis."[1 2]—I am, etc.,

London, W.1. DENIS BROWNE.

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## Dumping Syndrome

SIR,—I read with great interest the two papers on the dumping syndrome by Mr. L. P. Le Quesne, Mr. M. Hobsley, and Mr. B. H. Hand and by Mr. Hobsley and Mr. Le Quesne (*Journal*, January 16, pp. 141 and 147). They quote Machella[1] as showing that the symptoms of the dumping syndrome can be reproduced by the ingestion of hypertonic glucose. It is by no means certain that the symptoms so produced are those of the true dumping syndrome. If these symptoms do not constitute a natural or true attack of dumping, the investigators who use hypertonic glucose are merely investigating the reaction of the dumping patient to a particular stimulus. This reaction does not necessarily have any connexion with a naturally occurring dumping attack.

In investigating attacks of true dumping, i.e., attacks produced by giving to the patient those particular foods that the patient states bring on the attack, we have been unable to show any alteration in the plasma volume as measured by haematocrit estimations. This may well be due to the difference in aetiology between the true dumping attack and the dumping symptoms produced by hypertonic glucose. A paper is in preparation.—I am, etc.,

Manchester. H. T. COX.

REFERENCE

[1] Machella, T. E., *Ann. Surg.*, 1949, **130**, 145.

SIR,—I have read with interest the article by Mr. L. P. Le Quesne, Mr. M. Hobsley, and Mr. B. H. Hand on the dumping syndrome (*Journal*, January 16, p. 141).

In your leading article in the same issue (p. 179) you mention the practical steps which may be taken to prevent or diminish dumping. I should like to enlarge on this and mention four procedures which have been introduced to this end, in the treatment of duodenal ulcer by gastrectomy. These were the return to Billroth I, colonic replacement, jejunal replacement, and in my own cases the use of Y-anastomosis with Polya gastrectomy. I am assured that with the use of Billroth I vasomotor symptoms were considerably decreased, and that in the replacement operation vasomotor symptoms did not occur. When using the Y-anastomosis in a large series of cases we noted that vasomotor symptoms were negligible, and in those cases in which vasomotor symptoms followed the standard Polya gastrectomy and which have been subjected to Y-conversion, the vasomotor symptoms disappeared.

Mr. M. Hobsley and Mr. L. P. Le Quesne (p. 147) have put forward the hypothesis that the essential factor in the production of the dumping syndrome is a defect of carbohydrate metabolism. I do not think this is the whole story. It is my opinion that to the afferent loop of a Polya gastrectomy must be apportioned some of the blame. The four procedures I have mentioned which prevent or diminish vasomotor symptoms have a common denominator—namely, no afferent loop.—I am, etc.,

Princess Margaret Hospital, Swindon, Wilts. J. EWART SCHOFIELD.

## Blood Groups in Rheumatic Carditis

SIR,—It was with considerable interest that I read the paper by Drs. C. A. Clarke, R. B. McConnell, and P. M. Sheppard on "ABO Blood Groups and Secretor Character in Rheumatic Carditis" (*Journal*, January 2, p. 21). I became interested in the former aspect some time ago while working in the United Cardiff Hospitals at Llandough Hospital, Penarth.

When obtaining and cross-matching blood for mitral valvotomy patients, it seemed to me that there was some discrepancy in the frequency of the blood groups of these patients and the expected frequency of the area population. I was able to collect a series of 213 cases of mitral stenosis who were admitted to hospital for assessment with a view to mitral valvotomy—the vast majority of whom had the operation performed. In about half of the cases I determined the ABO and Rh blood-groups personally, and the remainder had been grouped previously using the same method in the same laboratory. The details of these latter cases were obtained from the records in the hospital in-patient notes.

Figures for the ABO groups of 213 cases of mitral stenosis for the Cardiff area are as follows:

| Blood Group | Number | Percentage |
|---|---|---|
| O | 90 | 42·2 |
| A | 86 | 40·4 |
| B | 25 | 11·7 |
| AB | 12 | 5·6 |
| | 213 | 99·9 |

At present I have no figures for a control series, but if the Cardiff figures are compared with those of the controls quoted by Clarke *et al.*, i.e., Group O 48.8%, Group A

39.2%, Group B 9.5%, and Group AB 2.5%, it will be seen that there is a tendency towards a decrease in the incidence of Group O patients with mitral stenosis compared with the other ABO groups. My figures also suggest, as had been observed by Dr. Clarke *et al.* in the paper by Glynn *et al.*[1] that in patients with mitral stenosis due to rheumatic carditis the incidence of Groups B and AB are rather high at the expense of Group O.

Of the 213 patients whose cells were tested with rhesus anti-D serum in albumin 174 (81.7%) were rhesus-positive and 39 (18.3%) were rhesus-negative. These figures do not suggest any variation from the frequencies encountered in any series of normal individuals.

Although no proof of an association between any ABO blood-group factor and rheumatic carditis can be obtained from the details so far published, I support Dr. Clarke and his fellow workers in their plea for large numbers in the field of research in the hope of establishing with statistical certainty whether or not there is such an association.—I am, etc.,

W. L. HOOPER.

R.A.F. Institute of Pathology and Tropical Medicine, Halton, Aylesbury.

REFERENCE

[1] Glynn, A. A., Glynn, L. E., and Holborow, E. J., *Lancet*, 1956, **2**, 759.

SIR,—We were interested in Dr. George J. Addis's letter on the above subject (*Journal*, January 30, p. 346). When our paper (*Journal*, January 2, p. 21) was submitted for publication we had not seen his data,[1] but we find that it is legitimate to combine his Glasgow figures with those from Taplow and Liverpool because there is no heterogeneity between the three centres with respect to the relative incidence of the disease in group O versus A, B, and AB combined ($\chi^2$ for two degrees of freedom=3.59, p=>0.1). All are in agreement in showing a deficiency of group O, and the addition of Dr. Addis's figures merely reduces our $\chi^2$ for one degree of freedom from 8.15 to 7.07, the probability that the association is due to chance still being less than 1 in 100. It seems, therefore, that there is a good prima facie case for an association between rheumatic fever and the ABO groups, the mean relative incidence of the condition in patients who are not group O being 1.16, with 95% confidence limits of 1.04–1.30. However, more data are obviously desirable, because, as we pointed out in our paper, the level of significance does not approach that needed before an association can be regarded as well-founded.

Dr. Addis comments on the work of Wilson and Schweitzer,[2] who claim to have shown that rheumatic fever is inherited as a recessive character controlled by a single gene with full penetrance. He suggests that this finding implies that any association between the disease and the ABO blood groups must be preponderantly with group O. If, however, the recessive is a gene also controlling these blood groups, then all rheumatic-fever patients would be of the same blood group (not necessarily O), which is known not to be the case. If the postulated relationship with blood group is due to linkage and selection, again there is no necessity for the association to be with group O.

Wilson and Schweitzer point out that the severity of the illness is influenced by other characters; and, if the ABO blood groups are involved, an association between one of them and rheumatic fever would be likely to be found when hospital patients (the severer cases) are examined. Here, too, there would be no reason to expect an association with group O.

With regard to Dr. Addis's point about controls, the relation between hospital patients and the general population (blood donors) in respect of the ABO groups has in fact already been defined, and we refer him to one of our earlier papers.[3]

Finally, the suggestion that there may be errors of blood typing among the A's, B's, and AB's does not affect our statistical analysis, since this is concerned only with the relationship of O to all the other groups combined.—We are, etc.,

C. A. CLARKE.
R. B. MCCONNELL.
P. M. SHEPPARD.

Liverpool.

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[3] Clarke, C. A., Cowan, W. K., Edwards, J. W., Howel-Evans, A. W., McConnell, R. B., Woodrow, J. C., and Sheppard, P. M., *Brit. med. J.*, 1955, **2**, 643.

## Names of Drugs

SIR,—Is it not time that we showed some sense of proportion in our nomenclature of drugs? Slavishly to call each drug by its official *B.P.* name, and not by the name given to it by its manufacturer, could easily result in confusion.

As far as I know only one firm manufactures halothane. As far as I know there is only one other company in this country which could manufacture it on a commercial basis, and it is extremely unlikely that this firm would ever bother to do so. Even if two brands of halothane were available, I should personally prefer to use the brand which I had learned by experience could be relied upon to be free from impurities. The manufacture of halothane is a difficult process, and I understand it is relatively easy for impurities to be present in the final product unless the most careful precautions are taken. I can see no merit in calling the substance we use in anaesthesia halothane rather than "fluothane."

Several companies manufacture thiopentone. If some unfortunate incident followed the use of a certain brand of thiopentone, it would be important to know which brand had been used, and therefore to write in the notes that a patient had thiopentone, nitrous oxide, and oxygen is not as instructive as to say that the patient had "pentothal," nitrous oxide, and oxygen, or "intraval," or whatever particular brand of thiopentone was used.—I am, etc.,

T. H. S. BURNS.

Department of Anaesthetics, St. Thomas' Hospital, London, S.E.1.

## Serum Gonadotrophin in Acne

SIR,—I have read with great attention the article by Dr. J. H. S. Pettit (*Journal*, February 28, 1959, p. 557), and after much reflection I feel I cannot leave without comment the categorical conclusions which he has drawn from a valueless clinical trial.

(1) Dr. Pettit does not specify the clinical type of eruption he is treating, and speaks of "acne predominantly of a comedone type"; if there are no comedones the condition is not acne, and serum gonadotrophin has no reason to be effective. (2) He has associated local forms of treatment which I consider harmful. (3) He asks his patients "to co-operate in an investigation to test the efficacy of a new drug," a factor which by itself is susceptible of influencing the results. (4) He reveals preconceived ideas which appear clearly in the section entitled "Method"; furthermore, the trial has been undertaken with a very incomplete documentation as judged by the list of references.

(5) Finally, his opinion is based on a statistically insignificant number of cases, and the result is therefore meaningless.

If Dr. Pettit had taken the trouble to consider the statistical value of his results he would have found that: $P \simeq 0.3122$, which is very much higher than the criterion of significance usually adopted of 0.05; the number of patients in the group receiving the gonadotrophin tablets being less than the percentage of failure of the method, all the results might have been negative or positive without permitting a conclusion as to the value of the treatment. The range of reliability of Dr. Pettit's results varies between 22% and 66%, which is much too wide if one wishes to keep a reasonable factor of safety. Moreover, the placebo technique should be considered with some restriction outside the psychosomatic field, and particularly in acne, since humans are not all identical (unlike pure-bred rats). To obtain statistically significant results with this method it is necessary to use large series.

My conclusions are based on 130 cases[1]; 114 cases[2]; 240 cases[3]; 130 cases[4]; 206 cases[5]; large enough numbers to be significant. As a control, I prefer to compare the effects of two different forms of treatment in the same subject: most of my cases have been controlled since they had previously been unsuccessfully treated with local applications, oestrogens, antibiotics, etc. In almost all of 303 patients I have treated by implantation, and 576 with transmucosal tablets, serum gonadotrophin has produced an improvement which is shown by a reduction of the seborrhoea and the hyperkeratosis associated with it. On the evidence provided, I cannot accept the dogmatic assertions which Dr. Pettit has made concerning the efficacy of serum gonadotrophin in the treatment of acne vulgaris.—I am, etc.,

Paris. R. ARON-BRUNETIÈRE.

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3. —— ibid., 1954, **61**, 143.
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## Psychogenic Disorders in Children

SIR,—Dr. John Apley (*Journal*, January 16, p. 191), invites comment on his enthusiastic experiment in child psychiatry. He considers that "in paediatric practice the tide of physical disorders is receding." Faced with time on his hands and the prominence of psychogenic disorder, he proposes that paediatricians should treat these patients and when they do not respond to "explanation and reassurance" by him, they should be referred to a psychiatric social worker for "diagnosis and treatment" and thus "avoid the necessity of transfer from one department to another." *En passant*, it is reasonable to wonder whether he proposes that paediatricians should now experiment in orthopaedic surgery, whilst referring the more difficult cases to the physiotherapist; it may be argued that medical training provides a better introduction to orthopaedic surgery than to psychiatry.

Dr. Apley has listed a number of disadvantages of his experiment and to these could be added the following:

(1) It is not clear how Dr. Apley differentiates a minor from a major problem. The extent of an emotional disorder cannot be judged from the extent of the presenting physical symptom. It is not clear from what source the necessary skilled and extensive knowledge of childhood psychopathology would come. Moreover, results cannot be judged by the relief given to symptoms. In child psychiatry, as in other branches of medicine, the aim is not to remove the warning indications of disorder, but to treat the underlying disorder itself.

(2) Contemporary psychiatry has long recognized that the assessment of children can take place only in relation to the assessment of the psychopathology of the parents. This essential evaluation, involving extensive experience of adult psychopathology, is absent from his plan.

(3) Dr. Apley denies his patients the skilled help of psychiatrists, conversant with child and adult psychopathology. Possibly the need for them has not been made apparent, but each specialty has difficulty in explaining its skills to others.

(4) It is not customary for a psychiatrist social worker to undertake diagnosis and treatment outside social case work. Furthermore, psychiatric social workers are in even shorter supply than child psychiatrists. The psychiatric social worker is likely to be most effective when working in collaboration with a child psychiatrist, a procedure of proven value.

(5) Dr. Apley may find it very difficult to prove that where psychiatric units for children have been established in "medical centres," then the rate of referral of children under five, or the failure rate for first appointments, is less satisfactory than for such children attending a paediatric clinic. In the town of Ipswich, for instance, the referral rate for children at the child psychiatric clinics of the Ipswich and East Suffolk Hospital shows that 20% of the children referred are under five. The failure rate for the first appointment at the same clinics was 1 in 14 in 1959, which compares very favourably with the ratio of 1 to 9 for all hospital clinics.

(6) A minority of children attending hospitals are referred to children's physicians. Is it to be expected that children's surgeons, E.N.T. surgeons, ophthalmologists, etc., are also to practise child psychiatry? If not, is it suggested that the children's physician should receive all children referred to hospital and undertake child psychiatry when he thinks fit? Does this not cut across the traditional and proper function of the general practitioner, which is to have continual care for the child and the selection of a specialist? I find that general practitioners are well aware of their responsibility for emotionally ill children and show no reluctance to seek psychiatric help when they desire it. In 1959 at the children's clinics mentioned above, 82% of the 407 new cases actually seen came from the general practitioner.

Many paediatricians are finding the answer to this situation by collaborating with the psychiatric units for children that are being rapidly developed in major hospitals. This collaboration makes for better all-round child psychiatrists and paediatricians and gives the latter, amongst other things, total assessment of the sick child, enhanced care of the handicapped and disfigured child, and a new outlook on the management of paediatric wards. Psychiatrists are well aware of the need for more child psychiatrists, and the Royal Medico-Psychological Association is encouraging the recruitment and training of child psychiatrists with the help of a responsive Ministry of Health. The position should soon be reached when there will be an adequate supply of fully trained child psychiatrists.—I am, etc.,

Ipswich and East Suffolk Hospital, Ipswich. J. G. HOWELLS.

SIR,—The article by Dr. John Apley and others (*Journal*, January 16, p. 191) will have aroused much interest amongst those engaged in hospital paediatrics. The authors invite comments from others and may like to hear something about our present attempts to

deal with a related problem here. In our case the direct co-operation is between psychiatrist and almoners.

Early last year Dr. A. C. Woodmansey, of the department of psychological medicine, offered to meet a small group of almoners from my department for discussion of current case material. With the approval of the physicians concerned and the director of the department of psychological medicine, a start was made in May, 1959.

The problem, as it seems to us, is that a great deal of the work required of the almoners involves meeting and dealing with emotional conflicts in parents which prevent their co-operating effectively in the treatment prescribed for the child. The care of sick children, particularly if they are seriously ill or chronically handicapped, may present many difficulties to the parents. The physical and emotional are entangled and in many cases interwoven with family problems. However much practical domiciliary help is given there is inevitably some parental anxiety and additional strain is placed upon the whole family, particularly if the child is being looked after at home.

The task of helping parents with these complicated problems associated with their child's illness has traditionally devolved on the almoner working in conjunction with the paediatrician, family doctor, and the social services outside the hospital. We have long had opportunities for informal discussion with members of the department of psychological medicine, particularly since there has been a psychiatrist available for consultation in the medical outpatient department. This further development of holding weekly seminars we have greatly welcomed; it is helping us to give a better service to the families, and in cases where the child and/or parents need psychiatric treatment they can be helped to accept this perhaps earlier than would otherwise have been possible. It is hoped to increase the number of seminars in order to make the service available to other almoners, and I understand that a report of the experiment will probably be published in due course.

How to provide the best possible service with the limited number of paediatricians, psychiatrists, and social workers is indeed a problem. By pooling our experiences we hope we shall move a little along the road to a solution.—I am, etc.,

The Hospital for Sick Children, Great Ormond Street, London, W.C.1. MARGARET MAYFIELD, Head Almoner.

SIR,—As a G.P. who has to cope untrained with a 33% average rate of psychogenic illness in his practice I welcome the emphasis on this aspect of medicine in the articles in your issue of January 16 by Dr. D. T. Maclay on "Boys Who Commit Sexual Misdemeanours" (p. 186) and by Dr. John Apley on "Psychogenic Disorders in Children" (p. 191). With regard to the latter article, I feel the major responsibility must be borne by the G.P., who alone knows the family background intimately. Most G.P.s realize, if few others do, that to carry out their responsibilities in this field effectively they will require training which the present archaic undergraduate and postgraduate education does not provide.

Doctors are slowly becoming aware that in contrast to traditional teaching a high percentage of such paediatric problems as asthma, headache, anorexia, vomiting, and abdominal pain have no physical basis whatever, and are due to the tension and stress caused by faulty parental attitudes. They are beginning to scrap such diagnoses as the old favourite of "mesenteric adenitis" in children complaining of abdominal pain without definite physical signs, and to realize that this syndrome is just as much a stress condition as duodenal ulcer and is often the forerunner of an ulcer in later life. If the stress-producing factors in family life were detected and treated by the G.P., sexual misdemeanours and juvenile delinquency would be considerably reduced and mental ill-health assume less alarming proportions.

It was refreshing to read in Dr. Maclay's article that "orthodox psychoanalytic treatment of the juvenile sex offender is not indicated and should be avoided."[1] It is to be hoped that the futility of Freudian-orientated therapy in all fields of psychiatry will become more generally realized and the scientific outlook of American therapists such as Karen Horney, Harry S. Sullivan, and Lakin Phillips more appreciated in Britain. In particular, Horney's concept of profound basic anxiety in the nervous child compelling him to develop either a compliant dependent character trend or an aggressive rebellious trend or an alternating blend of both is very helpful in undertaking children's neurotic reactions.

In conclusion I should like to comment briefly on the psychogenic aspects of migraine and hypertension (*Journal*, December 26, p. 1430). It is remarkable how many hypertensives have a history of stress-producing factors in childhood and later life. A boy of 14 in this practice beginning treatment for severe anxiety state has a diastolic pressure of 100 at rest, which in the absence of any organic lesion must be considered of psychogenic origin. After psychotherapy in this type of case a considerable fall in pressure can be expected. It is reasonable to suggest that the vascular spasm common to migraine and hypertension is primarily due to nervous tension, and in the earlier stages amenable to psychotherapy. Long-continued spasm of the renal arteries might well result in irreversible renal changes and permanent hypertension.

—I am, etc.,

Belfast. S. E. BROWNE.

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## Specialist Consultation

SIR,—This is to try to refute the common assumption that frequent reference of patients to hospital is evidence of a low standard of practice. This assumption was implicit in Dr. John Fry's recent account of his own practice (*Journal*, December 12, p. 1322), and it appears again in Dr. J. G. M. Hamilton's article in the *Supplement* of January 23 (p. 23). It might be more reasonably argued that the more carefully a case is studied the more difficulties are uncovered and the more the need for specialist help is felt. "A Case of Malignant Hypertension" in the *Journal* of January 23 (p. 262) exemplifies this argument perfectly.

On the contrary it may be that many patients are not referred when they should be, and in consequence morbidity and mortality are higher than they need be. Conversation with some senior practitioners has suggested that this is frequently the case.—I am, etc.,

Lincoln. W. PATRICK ROE.

## Pilonidal Sinus

SIR,—I do not believe that Mr. Denis Browne (*Journal*, January 23, p. 279) is correct in supposing that surgeons are confused as to what is a pilonidal sinus. An attempt was made at the Manchester meeting of the Association of Surgeons of Great Britain and Ireland to include the dural fistula under this heading, and was widely criticized in the ensuing discussion.

Surely, too, the term "jeep disease" does not explain its pathology, not to everyone's satisfaction. The type

of pilonidal sinus which occurs at the root of the nose can hardly be explained on these grounds. This variety, though not listed by Aird,[1] is typical in that it contains hair and is liable to secondary infection. It is usually dealt with in early childhood because it is so disfiguring. One so experienced in child surgery as Mr. Browne is presumably familiar with this rather rare form.—I am, etc.,

Wolverhampton. RONALD BENISON.

REFERENCE

[1] Aird, I., *Brit. med. J.*, 1952, **1**, 902.

### Ceiling of the Great Hall

SIR,—Although I am grateful to Mr. H. Austen Hall (*Journal*, February 6, p. 421) for his complimentary references to *Doctors' Commons*, I must point out that I did not mean to imply that Lutyens intended the Great Hall to remain ceilingless for ever. My impression was that Lutyens uttered the expostulation to the B.M.A.'s officers, " Leave the thing open," adding that they would grow to like it, in order to cut short what must have seemed to him a hopeless argument. He wanted the original design completed ; the B.M.A. wanted something simpler. The result has been a compromise which, as Mr. Austen Hall points out, has never really pleased anyone.—I am, etc.,

London, S.W.19. PAUL VAUGHAN.

### Alcohol and Road Accidents

SIR,—Dr. Guy Roworth (*Journal*, February 6, p. 419) so rightly draws our attention to the fact that temperament and general make-up are a great factor in the number of accidents nowadays. " Show me an ill-mannered driver, and I'll show you an accident-prone one " is only too true. Nowadays ill-breeding among car drivers is far more noticeable, probably because of the wider spread of cars into all groups of the population. We are therefore getting a larger number of drivers who have never had to bear responsibility or to show consideration for anybody but themselves.

The car-accident-prone group would be an excellent one for a G.P. field study, and might yield good dividends in lives, provided something could be done about these types. Dare one suggest psychiatric treatment ?—I am, etc.,

Stanley, Perthshire. OWEN MCDONAGH.

SIR,—If an instrument can be produced which accurately measures the percentage of alcohol in the blood, let it be used to convict suspects whose bad driving or erratic conduct has attracted attention. But I am loath to see the introduction of breath-testing for alcohol of those motorists whose behaviour has been inconspicuous. Such an innovation might reasonably be expected to lead to similar tests being carried out on pedestrians, who make a substantial contribution to road accidents. And, following on this, there would also have to be established tests and corresponding safety levels for drugs in the blood for those motorists and pedestrians who are taking sedatives, tranquillizers, insulin, and the like.

The Special B.M.A. Committee on Alcohol and Road Accidents is to be congratulated on its report, and few will disagree with its conclusions (*Journal*, January 23, p. 269). But what practical steps can be taken to reduce accidents due to the influence of alcohol ? It would be interesting to hear in what circumstances biochemical tests are applied in the countries which have adopted them, such as Norway and Sweden, and how their motor-accident rate in which alcohol is a factor compares with that in this country. Do they have a special corps of breath-alcohol-testing police or " breath-alyzer "-equipped wardens stationed in car parks, pubs, and restaurants ? Is the victim of the test selected haphazardly, or what are the indications for its application ? I can anticipate considerable resistance in this country to the introduction of biochemical tests unless they are applied after arrest in the case of those " suspected of a state of inebriety which gives reasonable cause for anticipating that an accident may occur." Then by all means convict if the percentage of alcohol in the blood exceeds something over 0.05, even if this may only have been occasioned by an intake of three small whiskies.

I believe that the alcohol-accident-rate could be reduced by increasing the rewards for sobriety and making the penalties for drunkenness progressively more severe. Some motor-insurance companies offer a considerable rebate in premium to teetotallers. This might be extended, and no-claim bonuses increased to 50%. On the other hand, a first offence should involve automatic disqualification ; the second, disqualification and substantial fine ; and the third, permanent disqualification and possibly imprisonment.—I am, etc.,

London, W.1. ELLIS STUNGO.

### Hypnotic Suggestion in Domiciliary Midwifery

SIR,—I read with interest Dr. J. W. F. Lumsden's letter on hypnosis in domiciliary midwifery (*Journal*, January 30, p. 350). It is in this field that hypnosis gives its most satisfying results. One criticism levelled against its use is that only a small proportion of the population can achieve a useful degree of trance. While this is true of the population at large, the family doctor can expect much more success in his own patients. There is already an established rapport, and in pregnancy the patient is especially responsive to suggestion. Since becoming interested in the subject, I have been impressed by the number of healthy people who can spontaneously enter a useful hypnotic state. The number could be greatly increased by education, training, and selection.

Quite apart from its use in controlling anxiety, increasing confidence and co-operation, it can be used to stop hyperemesis and other discomforts of pregnancy. It is the only safe anaesthetic, and the only one which can leave the patient feeling better after its administration than before. I think there is a case for testing as many as possible of one's practice for suggestibility, so that should the necessity arise they will know that they need not endure the risk or discomfort of the orthodox anaesthetic in minor—and sometimes even in major—surgery.—I am, etc.,

Dundee. R. A. B. RORIE.

SIR,—Dr. J. W. F. Lumsden expressed in his letter (*Journal*, January 30, p. 350) the view that domiciliary obstetrics could become a perfect example of team-work between the doctor, midwife, and the mother, if general-practitioner obstetricians would take the trouble to train their patients in hypnotic relaxation antenatally. I would like to add that in order that hypnotic relaxation and anaesthesia should be fully effective in domiciliary

midwifery it is necessary to train and instruct the midwife, so that she should know how to handle a mother who has been so conditioned. Any lack of co-operation and understanding between the doctor-hypnotist and midwife may adversely affect the success of hypnotic anaesthesia and relaxation, as hypnosis is based on a strong interpersonal relationship. I found too, like Mr. Lumsden, that a mother who has gone through a delivery under hypnosis gains permanently in self-confidence.[1]

These are the advantages of hypnosis used as an anaesthetic and analgesic in obstetrics, as compared with other methods: (1) Hypnosis is not a complicated procedure, it is easily learned. (2) No special apparatus or expense is involved. (3) There is no respiratory or circulatory depression in the mother or foetus, which may occur under chemical anaesthesia. (4) Hypnosis raises the resistance to obstetric shock. (5) There is no maternal exhaustion following delivery under hypnosis as the resistance to fatigue is definitely raised. (6) The pain threshold is effectively raised by the removal of fear and tension. (7) The blood loss is decreased during the hypnotic state. (8) The relaxation and analgesia obtained under hypnosis can be extended through post-hypnotic suggestions to the post-natal period There is complete analgesia in the sutured perineum and a total absence of after-pains. (9) The strong rapport established with the mothers during their antenatal hypnotic training is of great value post-natally. There is subsequently a closer medical contact between the doctor and mother and baby than in the cases delivered in hospitals without hypnosis.

Hypnotic anaesthesia is one of the safest methods of conducting painless labour. DeLee and Greenhill[2] stated, "The only anaesthetic that is without danger is hypnosis. . . . Psychiatrists claim that no person ever died under pure hypnosis. I have used suggestions a great deal, indeed almost constantly, and I am irked when I see how my colleagues neglect to avail themselves of this harmless and potent remedy."—I am, etc.,

London, S.E.25. A. FRY.

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[2] DeLee, J. B., and Greenhill, J. P., *Yearbook of Obstetrics and Gynaecology*, 1939, p. 164. Chicago.

## Cauda Equina Syndrome

SIR,—The paper by Mr. R. H. Shephard in your issue of December 26 (p. 1434) is a most valuable one. The cauda equina syndrome from massive extrusion of disk material is, as he says, not at all uncommon.

Two aspects have been apparent to me, and, I think, merit stressing: firstly, however soon after massive extrusion of disk material one operates, recovery is very tardy (cf. after removal of a cauda equina tumour) and so often incomplete. One assumes that this is due to some irritant effect of disk material on nerve roots. I recall one man who complained of paralysis and anaesthesia of both legs immediately after a spinal manipulation under anaesthesia ; at laminectomy exactly ten hours later a large extruded fragment was removed. There was insignificant recovery when I last saw him three months later.

Secondly, of the four cases of this syndrome which I have encountered personally, two followed immediately upon a spinal manipulation under anaesthesia. I have been so impressed by the seriousness of this misfortune as to make it a rule never to manipulate in the presence of objective root signs, motor or sensory. Furthermore, where objective root signs have first appeared after a manipulation (usually with increase in pain) or have been aggravated by that procedure, I have preferred to proceed to surgery instead of alternative conservative treatment. I would be most interested to know of the experience of your readers on these aspects of the cauda equina syndrome.—I am, etc.,

Bulawayo. A. T. MATHESON.

## Polio in Europeans in West Africa

SIR,—From this hospital there has recently been flown to the United Kingdom a young European with poliomyelitis, on a respirator and attended by a medical and nursing team. Three weeks before a team of doctors and nurses with a respirator had flown to the north of Nigeria to bring this young man into hospital here. When he arrived he could move only the muscles of the eyes and lids. During the three weeks it has been my privilege to watch the treatment of this young man, which I do not think could have been bettered in any other hospital that I know of. When he left here this patient was able to use his facial muscles, could move fingers and toes, and could be independent of the respirator for about four minutes at a time. This kind of case is met with not infrequently here, always in Europeans ; sometimes the outcome has been less encouraging.

Poliomyelitis is virtually unknown in the adult West African, although the late effects of " infantile paralysis " are seen from time to time in children. It seems likely that the indigenous population becomes immunized in early childhood as a by-product of the primitive sanitary and overcrowded living conditions. That such a state of affairs exists in North Africa is suggested by the studies of Paul and Horstmann[1] and in French West Africa by Said, Drouhet, Soulé, and Celers.[2]

That is one side of the picture. Another is that I have seen in the course of work in the medical out-patient clinic here a number of Europeans recently come to this country who have not been inoculated against poliomyelitis. While travelling here, by sea, I made inquiries of fellow passengers, quite a number of whom were young adults coming to West Africa to teach or to escape the English winter by visiting relatives here. It was a surprise to find that many had not been inoculated. Lagos is only twelve hours by air from London, and one reads almost daily in the local newspaper of visits of trade delegations and commercial representatives from Europe. One wonders whether all these persons realize the risks they may be running. It is possible to get prophylactic inoculation against poliomyelitis in Nigeria, but not, of course, as easily as in the United Kingdom. The whole question of the inoculation of visitors and temporary residents is to be taken up here with the Federal Ministry of Health. In the meantime it cannot be too strongly emphasized that prophylactic inoculation against poliomyelitis should be regarded as essential for any European coming to Nigeria even for the briefest of visits.—I am, etc.,

University College Hospital, Ibadan, Nigeria. HAROLD SCARBOROUGH.

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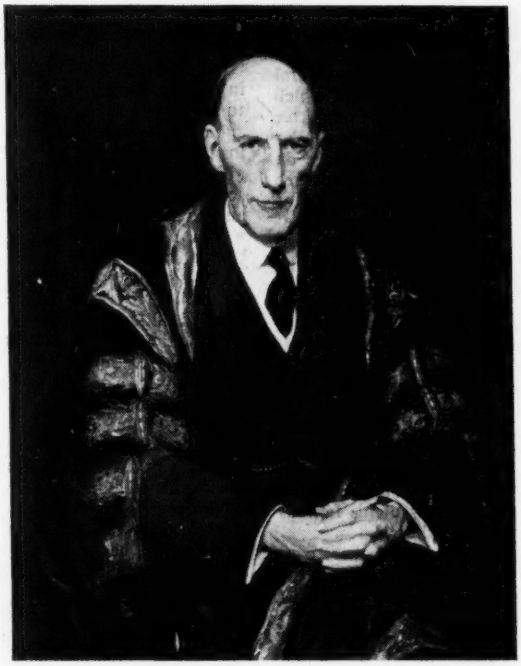
# Obituary

## Sir ROBERT HUTCHISON, Bt., M.D., LL.D., D.Sc. F.R.C.P., Hon.F.R.C.P.Ed.

We record with great regret the death of Sir Robert Hutchison on January 12 at his home in Streatley, Berkshire, at the age of 88. A Past-President of the Royal College of Physicians, he was consulting physician to the London Hospital and the Hospital for Sick Children, Great Ormond Street. His *Clinical Methods* and other well-known textbooks have occupied favoured places on the bookshelves of doctors for many years.

Sir Robert Hutchison was not only a great physician but a man of letters and a man of affairs. He was every inch a Scot—and his inches were many—who won his reputation in the South by sheer force of mind and character, without surrendering the dourness which came with his Lothian blood. His intellect was matched by his integrity, and they were both illumined by a wit that though often razor-sharp was always kindly.



Robert Hutchison was born at Kirkliston, West Lothian, a few miles from Edinburgh, on October 28, 1871, the youngest of seven children of Robert Hutchison and Mary Tait. His father was nominally a wine merchant, but really a country gentleman interested in agriculture and arboriculture. At the age of 6 Robert Hutchison announced his firm intention of becoming a doctor, though he had no medical relatives or ancestors except Sir James Wylie, Bt., a great grand-uncle, who was head of the Russian Military Medical Service at the beginning of the last century and who accompanied the Czar Alexander at the time of Napoleon's retreat from Moscow. He was educated at the Collegiate School, Edinburgh, now extinct, and matriculated as a medical student at the University of Edinburgh when barely 17. Because his father had fallen into financial difficulties he had to pay for his education by bursaries and scholarships, and on graduating M.B., C.M. with first-class honours, in 1893 at the age of 21 he was awarded the Ettles scholarship, granted to "the most distinguished graduate of the year."

The day Robert Hutchison was "capped" he entered the Simpson Memorial Hospital, Edinburgh, as house-surgeon and conducted a delivery that night. Later he became house-physician to Professor Greenfield at the Edinburgh Royal Infirmary and house-physician at the Sick Children's Hospital, Edinburgh: as a student he had been a pupil of John Thomson and acquired from him an interest in children's diseases. In the autumn of 1894 Hutchison went to the University of Strasbourg to study "physiological chemistry," as it was then called, under Professor Hoppe-Seyler, and he also spent some weeks in Paris visiting various hospitals. On returning to Edinburgh he was appointed assistant to Professor William Rutherford in the physiology department of the university. In 1896 he proceeded M.D., and in the same year took the M.R.C.P. of Edinburgh, and in the following year the M.R.C.P. of London. Not liking the work with Professor Rutherford, he resigned his appointment after a year and decided to move to London, where he arrived in October, 1896, with the proverbial half-a-crown and a few introductions. Largely through the influence of John Thomson he was appointed house-physician at Great Ormond Street Hospital, with Barlow, Lees, and Penrose as his chiefs. During that winter he wrote *Clinical Methods* in collaboration with H. Rainy.

After six months at Great Ormond Street he was appointed assistant to Dr. (later Sir) Leonard Hill at the London Hospital Medical College, where Hill was lecturer on physiology, Arthur Keith on anatomy, and William Bulloch on bacteriology. At the same time Hutchison went into residence at Toynbee Hall, where he remained four years. From the summer of 1897 until the beginning of 1900 he worked under Hill, teaching and conducting research on the thyroid and on diet. His book *Food and Dietetics* was published in 1900, the substance of it having been given in lectures at the London Hospital and in University Extension Lectures in the East End. Early in 1900 he was appointed assistant physician to the London Hospital and to Great Ormond Street Hospital. Two years later he moved to the West End of London and began private practice as a general physician, but with special leanings towards digestive disorders and to diseases of children. Though he said himself he never was a "pure" paediatrician, he was in the first rank of those who built the British school of paediatrics. In the first world war Hutchison was medical adviser to the Ministry of Food, his special concern being with the rations allowed for invalids.

He resigned from the staff of the London Hospital (where he was generally known as "Bobby Hutch") in 1934, having completed twenty years as assistant physician and fourteen as full physician, being then elected consulting physician. In the same year he gave up his appointment at great Ormond Street, having served his full time on the staff. He was created a baronet in the Birthday Honours of 1939, and in the following year, after his home had been bombed, he left London and retired to Streatley in Berkshire.

Hutchison was elected a Fellow of the Royal College of Physicians of London in 1903, at the age of 32. In the following year he delivered the Goulstonian lectures, on the anaemias of infancy. He was Harveian Orator in 1931. After Lord Dawson of Penn had completed seven years in office as President of the College, Hutchison was elected to succeed him in 1938. It was a difficult time. There was a feeling among the younger Fellows that the policy and affairs of the College were too much in the hands of the senior Fellows, especially of those in London. One of Hutchison's first steps, therefore, was to persuade the College to alter some of the by-laws so as to ensure a more open election to the council and a greater representation on it of Fellows from the provinces. It was also arranged that the council should meet every month and not at long intervals as hitherto, and some powers previously vested in the President were transferred to the council. The whole

machinery of the College was thus rendered more "democratic" and efficient. It took time to effect these changes, and they had hardly been introduced when war broke out. The ordinary activities of the College, however, went on, but much of the President's time was taken up with meetings concerned with the war. Sir Robert missed only one College committee during his period of office. Having held office for three years he did not seek re-election.

A member of the B.M.A. for 65 years, Sir Robert Hutchison not only accepted the offices which would inevitably be offered to a man of his distinction, but he sought actively to encourage other medical organizations to co-operate with the B.M.A. in its dealings with the Government and in plans for post-war reform. Always a great supporter of the scientific activities of the Association, he attended the Annual Meeting at Montreal, in 1897, as secretary of the Section of Physiology, and in Toronto, in 1906, he was secretary of the Section of Medicine. He was once vice-president of the Section of Pharmacology and Therapeutics (1910), twice vice-president of the Section of Medicine (1913 and 1932), and three times president of the Section of Paediatrics, at Bath in 1925, at Winnipeg in 1930, and at Melbourne in 1935. He served on several central committees, including the Nutrition Committee, which produced a report of great usefulness, the Aliens Committee (of which he was chairman), and the Central Medical War Committee. After his retirement he continued to serve on the committee of management of the Medical Insurance Agency, being chairman for a time, and on the council of the Medical Protection Society. He was on the board of the Royal Berkshire Hospital at Reading until the National Health Service began in 1948.

In addition to *Clinical Methods*, which reached its 13th edition in 1956, and which has been translated even into Chinese, Hutchison wrote *Food and Dietetics*, the 11th edition of which appeared in 1956, *Lectures on Diseases of Children* (9th edition in 1944) which has been translated into Russian and Persian among other languages, and several other books. He also edited the well-known *Index of Treatment* (13th edition in 1948), and was one of the group —sometimes called "the gang"—who under Osler founded in 1907 the Association of Physicians and the *Quarterly Journal of Medicine*, of which he was one of the editors for many years. Over the years new editions of his famous books have been prepared by younger authors.

He was elected to the honorary Fellowship of the Royal College of Physicians of Edinburgh in 1931 and to the presidency of the Royal Society of Medicine in 1934. The portrait by James Gunn here reproduced was presented to him at a ceremony at the Royal Society of Medicine in 1939. Sir Robert was an honorary LL.D. of Edinburgh and Birmingham, an honorary D.Sc. of Oxford, and an honorary M.D. of Melbourne. When he attained the age of 80 in 1951 the *Archives of Disease in Childhood* published an issue in his honour, and a hand-list of his writings contained therein shows 14 books and over 260 other writings. One of the last of these was "Medicine To-day and Yesterday—a Retrospect," which he contributed to the "Fifty Years of Medicine" number of the *British Medical Journal*.

In his teaching, in his consultations, in all that he did Hutchison combined conservatism with the open outlook. He was not quick to detach himself from old methods, but, on the other hand, he never without scrutiny put aside new claims even from unorthodox sources. He thought it usually wise to be a little behind the fashion in matters of treatment. Most of all he despised faddiness—one of the worst vices, he said, that could beset the therapist. A sense of proportion and a sense of humour were the great safeguards against it. A doctor should pull himself up, he said, when he found himself recommending the same kind of treatment for every sort of ill. Drugs, he thought, could certainly be used too much, but "they sometimes cured, they often relieved, they always consoled."

As a public speaker, though he divested himself of all oratorical frills, he was one of the most attractive in the medical profession. He spoke only when he had something to say, and he said it in the fewest words. His flashes of wit, his epigrams and apposite quotations, were all the more appreciated because of his quiet and restrained delivery and his rather solemn countenance, which he managed to maintain even when in jesting mood.

From the age of 18 to 48 he had intermittent attacks of duodenal ulcer: this was completely and permanently cured by a gastro-jejunostomy performed by the late Mr. James Sherren. Unfortunately he did not have a long period of good health after his operation, because at about the age of 52 he began to suffer from early symptoms of progressive muscular atrophy (amyotrophic lateral sclerosis); this progressed very slowly, but was a considerable handicap for the rest of his life. He never cared for games, and his chief recreations were travel and reading.

In 1905 Robert Hutchison married Laetitia, elder daughter of the Very Rev. Moore-Ede, D.D., later Dean of Worcester. She had graduated in medicine from the London Hospital shortly before her marriage. The celebration of their golden wedding a few years ago was a joy to all their friends. Sir Robert Hutchison is survived by his widow, two sons, both in the legal profession, and a daughter.

We are indebted to Dr. DONALD HUNTER for the following appreciation: In Robert Hutchison Scotland presented to England a young man who was destined to become a superb physician, an eminent scholar, a great writer, a most inspiring teacher, a shrewd and gifted clinician, and above all a most kindly gentleman. Although his career was so outstanding and successful he remained always modest and unassuming. He inspired real affection in those with whom he worked. His shafts of wit sent home his teaching points and his powers of instruction inspired a large number of physicians and paediatricians. Throughout his long life he never recovered from his surprise that, having come from Edinburgh as a young man, he was elected to the staff of the London Hospital.

In order to think of him at work one has to conjure up a tall, slightly stooping, rather gaunt figure, dignified and somewhat austere, but a little sorrowful. His features were aquiline, but he had a great liveliness of facial expression. His attitude was striking and dignified, somewhat suggesting that of a prima donna, although, of course, the bearing was in no way effeminate. His mode of thought was strikingly accurate and judicial, and often his choice of words was most fastidious. And then, of course, in the true Scottish tradition he had a beautiful command of English which made his lectures a joy to listen to and lent great power to his sarcastic wit. He was aware of his position and well conscious of his dignity and of his Scottish upbringing. At a dinner to Scotsmen in London he said: "A characteristic of Scotsmen not generally known is that they make first-class use of second-class brains."

### Some Remembered Sayings

Sometimes at Great Ormond Street he referred to his clerks as "a curious collection of crapulous cretins creeping from crib to crib." At the London he was content to call them "tabetic snails" or "desiccated frogs." In his ward teaching again and again he would insist upon gentle palpation of the abdomen and light percussion of the chest. When a new clerk percussed a child's chest he would say, "Hoots, toots, mon, stop! There you go hammering away at the chest, leaving behind you a trail of broken ribs. You're supposed to be percussing this child's lungs, not the cellars in the basement." He used to say: "Rheumatic fever is a disease which is commoner in what some ironical humorist has called the working class." On one occasion he was annoyed at being given a whole bunch of clinical laboratory reports. "These laboratory pundits think of me as a senile, doddering idiot, incapable of making up my mind, followed around the wards by an achondroplastic house-physician, microcephalic clerks, and a myxoedematous sister." In a letter to a friend he wrote, "At least never let anybody start a lecture in my memory. As I have said elsewhere, 'There are better ways of commemorating the dead than by boring the living.'"

Although his contributions to medicine have been considerable and his reputation extends far beyond Great Britain, it is his wisdom, absolute integrity, intellectual honesty, and sound clinical judgment more than any other qualities which have impressed themselves upon all who have known him, commanding their admiration and respect. He was not cynical, but he detested humbug and rather enjoyed holding up to ridicule anything that he felt deserved to be exposed. His criticisms, however severe, were accepted readily, for they were seldom unjustified, and they formed a most valuable part of the training he so gladly gave to his housemen. His grave manner with students was sometimes held up to criticism in contrast to the gaiety of Dr. Henry Head. But whereas it is true that usually he seemed too occupied with the matter in hand to give way to levity, to say that there was nothing gay in him was to misunderstand the man. He was in some ways a *poseur*; he *assumed* an air of complete cynicism. He hoped, so he pretended, that all things were for the worst, but this attitude was assumed, and behind it all was a mind intellectually gay with a cordial distaste for the earnest and the dull. "A dull dog" was a phrase which he applied to certain men, and in doing so he often maligned the dog.

Throughout a period of nearly 60 years Robert Hutchison was a prolific, instructive, and witty writer, and innumerable letters appeared under his name in medical journals. In 1934 in the "Battle of the Barbiturates" he wrote: "They contend that the barbiturates are a ready and increasing means of suicide. Well, Sir, what of it? So is the gas-oven, but no one proposes that the sale of gas-ovens should be restricted to doctors." Two of his textbooks were best sellers. *Clinical Methods* became known as "the bible of the Membership examination." His well-known *Lectures on Diseases of Children* is written in a terse and elegant style and is a book which should be in the possession of every doctor. What it sets out is as valuable now as when it was first written, for it records the ripe experience of an accomplished physician.

All who were privileged to know Sir Robert Hutchison must remember with pleasure many of his sayings. Thousands more who never met him can revel in the dry humour of his writings. Letter-writing he kept up until long after he retired from practice. Thus in 1953 in a letter entitled "Modern Treatment" he wrote:

> "I think there should be a new petition in the litany to be read in hospital chapels or wherever doctors and nurses do, or ought to, congregate. It might be as follows: 'From inability to let well alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, science before art, and cleverness before common sense; from treating patients as cases, and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us.'"

### Inspiration and Help

As an erudite physician Bobby Hutch taught us many things, but also as a philosopher he helped us to discover how all these things were good to know and worthy to be told. Always we deeply admired his scholarly approach, and we regarded him as the outstanding figure of contemporary medicine. We are proud to have been his pupils. At the London we remember so well how he stood tall and elegant in his frock-coat with one hand on the curtain rail above the patient's bed. Sometimes he lashed us with the irony of his clever tongue, but always he inspired us and helped us with full measure of his Caledonian common sense. And now with students and patients of our own alike in the lecture-room and in the sick-room his example is a constant help to us. Though naturally wishing we could have been more apt pupils, we shall continue to instruct the young in the methods for which he became famous. Robert Hutchison has left us to join those other giants of the London Hospital, William J. Little, James Parkinson, Jonathan Hutchinson, J. Hughlings Jackson, Waren Tay, James Mackenzie, Henry Head, and Hubert M. Turnbull. Not only men and women of Great Britain and the Commonwealth but all doctors the world over now mourn his loss. And all those whom he taught must feel the truth of that sentence in the Oath of Hippocrates: "I swear by Apollo and Aesculapius to reckon him who taught me this Art equally dear to me as my parents." For Lady Hutchison and her children and grandchildren we, his pupils, feel the deepest sympathy.

We are indebted to Dr. BERNARD SCHLESINGER for the following tribute: As one of his house-physicians at the Hospital for Sick Children, Great Ormond Street, and subsequent colleague, I would like to pay tribute to Robert Hutchison, whom I admired so much. In his heyday paediatrics had not yet developed into an extensive specialization, and he was able to bring to the subject his wide knowledge and experience of general medicine, which he practised concurrently.

He was a master at debunking loose thinking and extravagant flights of fancy. In committees, through a few refreshing, well-chosen words, appropriately salted with a dry Scottish wit, he succeeded in terminating tedious debates and often provided a quick and satisfactory solution. Some would argue that he was reactionary, but that came only in his later years. His approach to medical problems was always straight to the point, and this was well reflected in his concise style of writing. In this he inherited the mantle of John Thomson, whom he always admired, and he was also influenced by the works of Oliver Wendell Holmes. But he was a power unto himself, and his *obiter dicta* are still remembered with amusement by the various residents of his days.

Child guidance had not yet assumed its present-day position, but in a way he anticipated it. When confronted by a difficult child, he made the classical remark, "It is a clear-cut case of bromide for the mother." His reaction to the vast amount of advice given on infant feeding in the early days of paediatrics, often strangely contradictory, was that "all that needs to be known about it can be written on the back of a penny postage stamp." It was this simple, straightforward, and human attitude to life that attracted our affection and esteem.

With his death the last of the great physicians of the past has vanished from the field of medicine, but his spirit and the good he did for sick children remain. Walking round the old Alexandra Ward at Great Ormond Street, now usurped for other needs, I can imagine seeing a tall, gaunt figure, dressed in a grey frock-coat, taking a sniff at some fragrant flower before putting it in his buttonhole and saying, "Thank you, my dear" to the little girl who by custom presented it to him every Monday morning when he entered his ward.

## W. L. A. HARRISON, *M.C.*, M.R.C.S., L.R.C.P.

Dr. W. L. A. Harrison, who was formerly in practice in West London, died at his home on December 2, 1959. He was 67 years of age.

William Llewellyn Aplin Harrison, the son of Dr. Thomas Harrison, was born on September 1, 1892, in the house at Shepherd's Bush Green in which he died. He was educated at St. Paul's School and St. Mary's Hospital, qualifying in 1916. A great rugby-football enthusiast, he played for the Old Paulines and St. Mary's Hospital, and never missed an important match at Twickenham. During the first world war he served at first as a captain in the R.A.M.C. with the East Surrey Regiment, being awarded the *M.C.* Later in the war he served as medical officer to the Welsh Guards. On his return to civilian life he took over his father's practice in Shepherd's Bush, where he remained until his death. His sense of loyalty to friends and colleagues was strongly developed, and the badges of the East Surrey Regiment, St. Mary's Hospital, and St. Paul's School occupied a place of honour in his consulting-room.

In his young days Dr. Harrison took a keen interest in the stage, having a magnificently trained voice, and he took part in many theatrical enterprises, appearing on occasions with the late Ronald Colman. Music was always one of

his serious interests, and at the time of his death he was chairman of the Philharmonia Orchestra. When he became too old to play rugger, he took up golf and formed the Broad Acres Golfing Society, popularly known as "The Bags," acting as secretary for many years.

A fellow officer writes: Harrison and I served together in France and Italy in 1917, and he was always a most popular and regular attendant at dinners of the O.C. Association of the 12th (Bermondsey) Brigade of the East Surrey Regiment. He was the liveliest and grandest of medical officers, known to the brigade as "Mad Jack" because of his cold-blooded courage in rescuing wounded men in a dozen actions. The official history of the battalion records the tremendous gallantry and cheerful nonchalance he displayed when everything looked hopeless—and, happy man, it required no effort on his part. At Town Hamlets, where we lost 14 of 18 officers and 287 of 447 men, he turned a succession of German pill-boxes into dressing stations and saved innumerable men who were destined to die. He infused the will to live in very many cases who had "given up" (as men did at Passchendaele). If the C.O. had lived "Doc." Harrison would have received a considerably higher decoration than the *M.C.*

## D. S. BRYAN-BROWN, M.B., B.Ch.

Dr. D. S. Bryan Brown, who was a medical missionary in China before he went into practice in the north of London, died suddenly at his home in Enfield on January 23. He was 72 years of age.

Douglas Stephen Bryan-Brown was born at Amberley, Gloucestershire, on April 4, 1887, the son of the Rev. Willoughby Bryan Brown, and was educated at Eastbourne College, Downing College, Cambridge, and St. Thomas's Hospital, qualifying in 1912. After holding the posts of casualty officer and senior ophthalmic house-surgeon at St. Thomas's, he graduated M.B., B.Ch. in 1914, and in the same year went out to Peking, working for the Society for the Propagation of the Gospel. During the first world war he was acting medical officer to the British Legation in Peking, and after the war he went to Tatung in the north of Shansi Province. Here he became the first medical superintendent of the Mosse Memorial Hospital.

On returning to England in 1927 he went into general practice in Stoke Newington, remaining in that district as a respected doctor until his retirement in 1958. He was chairman of the City Division of the B.M.A. in 1944–5. During the second world war he was medical officer at the Woodberry first-aid post, and when the war ended he was elected to the Stoke Newington Borough Council, of which he was a distinguished member, being for three years chairman of its public health committee and also for a time a member of the L.C.C. divisional health committee.

M. M. writes: Throughout his residence in Stoke Newington Douglas Bryan-Brown was connected with the religious life of the borough, being attached for many years to St. Andrew's Church, Bethune Road. He became a lay reader in the diocese many years ago and more recently was connected with the Parish Church of St. Mary's. In 1959, only a few months after his retirement from medical practice, he was ordained deacon by the Bishop of London in St. Paul's Cathedral, and later that year, just a month before his death, was ordained priest. He had meantime moved to Enfield and become deacon at St. Thomas's Church, Southgate, serving faithfully until his death. In addition to his devout religious beliefs, Douglas Bryan-Brown was a true Christian socialist and an enthusiastic member of the Socialist Medical Association, having at one time been the chairman of its North London branch.

His wife, two sons, and daughter, who survive him, and his many friends will mourn the passing of a forthright and sincere human being. All who had the privilege to know him will rejoice that he was spared to realize his ambition and to bring to a conclusion the studies and devotion which prepared him for his ordination into the service of the Church.

## O. A. HEMPSON

Mr. O. A. Hempson, who was formerly solicitor to the British Medical Association and to the Medical Defence Union, and whose firm retains those appointments, died in Natal, South Africa, on February 5. He was 75 years of age.

Oswald Arthur Hempson was born on February 11, 1885, the second son of the late Mr. William Ernest Hempson, who for many years was solicitor to the B.M.A. He was educated at Sherborne, and, after spending a period in France, was articled to his father, being admitted a solicitor in 1909. During the first world war he served in the Artists Rifles and was later commissioned in the Royal Artillery. After the war Oswald Hempson was taken into partnership by his father and worked closely with him on the legal work of the Association and of the Medical Defence Union, to which his father also acted as solicitor. Upon the retirement of Mr. W. E. Hempson the two appointments were given to his firm and the major part of the work connected with them was undertaken by Oswald Hempson. The work was mostly of great responsibility, and often very complex questions had to be settled. Nevertheless the advice he gave was always straightforward and easily understood, and many important matters were successfully dealt with by him on behalf of the Association. His help was invaluable in organizing opposition to the Bill promoted in Parliament on behalf of osteopaths.

In addition to his work on behalf of the Association and many medical organizations and societies, Oswald Hempson acted for the Law Society in connexion with disciplinary proceedings against solicitors. He also carried out the legal work in connexion with the incorporation of the Royal College of Obstetricians and Gynaecologists. One of his famous court cases was the defence of Colonel Rutherford when charged with the murder of Major Seaton.

He was a sound lawyer, a wise adviser, and a good and persuasive advocate. He frequently appeared in the latter capacity before the General Medical Council and the Solicitors' Disciplinary Committee. A tireless worker, he never spared himself, with the result that the extra burden which fell upon him during the last war impaired his health. He took a prolonged holiday in South Africa and later decided to make his home there, finally retiring from practice in 1959.

Oswald Hempson married first Violet Hilda Day, who died in 1940, leaving two daughters and a son. He married secondly Sibyl Robertson. She survives him together with the children of the first marriage.

Dr. H. GUY DAIN writes: It has come as a shock to hear of the death of Mr. Oswald Hempson, who for a long spell was a very good friend, as well as a legal adviser to the B.M.A. The firm of "Hempson's" solicitors, acting on our behalf, has acquired an unrivalled knowledge of the legal problems and difficulties that may beset doctors either as individuals, perhaps requiring to be steered through the pitfalls of a partnership or assistantship agreement, or as an Association, with its numberless legal problems, both outside or within the Health Service.

In the early ninteen-twenties Oswald's father was many times to be seen a figure on the platform at the Representative Meeting answering questions and advising. On the retirement of his father Oswald took over the responsibility of legal adviser to the B.M.A. It was at once evident he was familiar with the history and the problems that were submitted to him for consideration. This knowledge, with his wise and balanced opinions, was of the greatest possible service to the Association through the years of National Health Insurance.

Mr. Oswald Hempson's distinguished presence, always immaculate, and complete with eyeglass and very friendly smile, will not easily be forgotten.

# Medical Notes in Parliament

### Minister Outside Cabinet

Mr. L. A. PAVITT (Willesden, West, Lab.) asked the Prime Minister on February 9 if, in view of the negotiations with the medical profession after the publication of the Report of the Royal Commission on Dentists' and Doctors' Remuneration and the importance of the Government's decisions arising therefrom, he would enlarge the Cabinet by the inclusion of the Minister of Health.

Mr. R. A. BUTLER, who replied, stated that Mr. Pavitt would be wrong if he thought that, because the Minister of Health was not a member of the Cabinet, the Government would give less than due attention to the questions raised by this Report. Mr. PAVITT asked Mr. Butler to use his very impressive persuasive qualities on the Prime Minister to urge him to take into consideration, not only the Government's position *vis-à-vis* the Minister, but in view of these negotiations with the medical profession the need for confidence on the other side in the negotiations if the outcome was to be satisfactory. The Royal Commission's Report might well set the pattern of the family doctor service for the next twenty years. The way in which previous negotiations were carried on had destroyed the confidence of the medical profession. This single act perhaps would be sufficient to restore confidence in the Government. Mr. BUTLER replied that the question would have done a service if it drew attention to the fact that the Government attached the greatest possible importance to this Commission and to its findings. He could assure Mr. Pavitt and the House that this matter would be treated by the Government as one of the first importance.

### Health Service Personnel

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) asked the Minister of Health on February 8 the number of personnel, other than medical and nursing staff, employed in hospitals in England and Wales when the National Health Service came into operation in July, 1948; and the number at the latest convenient date. Mr. D. WALKER-SMITH.—In round figures 197,000 at the end of 1948, and 250,000 at the end of 1958. This includes professional, technical, works, maintenance, domestic, administrative, and clerical staff.

### Smallpox and Vaccination Mortalities Compared

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked the Minister on February 10 for the total number of deaths during the last 20 years from smallpox and from smallpox vaccination, respectively, in Great Britain. Mr. WALKER-SMITH said that in 1939–58 there were in Great Britain 89 deaths from smallpox. During this period 151 deaths were attributed to complications following smallpox vaccination. He regretted that information about the number of persons vaccinated in this period was incomplete.

Mrs. BUTLER also asked for the total number of deaths during the last 20 years from smallpox and from smallpox vaccination of children up to the age of 5. Mr. WALKER-SMITH replied that there were in Great Britain in the period 1939–58 three deaths from smallpox of children up to the age of 5 years. During this period 103 deaths were attributed to complications following vaccination.

### Multiple Sclerosis Research

Mr. WALKER-SMITH stated in answer to Mr. D. PRICE (Eastleigh, Con.) on February 1 that the Medical Research Council was spending about £9,000 specifically on research on multiple sclerosis this financial year, and research was also taking place with the support of university funds and hospital endowments at other centres. Contributions from other sources, he understood, included expenditure of £40,000 over the last four years by the Multiple Sclerosis Society, and grants of over £27,000 by the Nuffield Foundation to be used over a period of five years.

# Vital Statistics

### Influenza in England and Wales

There were 36 deaths (23 of them in people aged 65 or over) from influenza during the week ending February 6: the figure for the corresponding week last year was 144. The pneumonia notifications and deaths were 467 and 682 respectively, compared with 944 and 986 in 1959. Bronchitis deaths fell from 718 in the week ending January 30 to 705 in the week ending February 6 (1,362 in the corresponding week last year). New claims on the Ministry of Pensions and National Insurance have also been falling slowly since the week ending January 5.

### Infectious Diseases

*Areas where numbers of notifications were high in the latest two weeks for which figures are available*

| | Week Ending | |
|---|---|---|
| **Measles** | Jan. 30 | Feb. 6 |
| Kent | 55 | **136** |
| Dover M.B. | 40 | **92** |
| **Dysentery** | | |
| Bedfordshire | 1 | **58** |
| Luton R.D. | 0 | **54** |
| Dorsetshire | 6 | **49** |
| Portland U.D. | 2 | **40** |
| Essex | 41 | **51** |
| Romford M.B. | 0 | **12** |
| Saffron Walden M.B. | 5 | **10** |
| Kent | 34 | **58** |
| Deal M.B. | 29 | **51** |
| Lancashire | 343 | **330** |
| Bolton C.B. | 21 | **43** |
| Liverpool C.B. | 25 | **41** |
| Oldham C.B. | 106 | **66** |
| Preston C.B. | 30 | **22** |
| Leigh M.B. | 18 | **27** |
| Swinton and Pendlebury M.B. | 33 | **16** |
| Worsley U.D. | 11 | **30** |
| Lincolnshire | 6 | **28** |
| North Kesteven R.D. | 1 | **22** |
| Middlesex | 33 | **76** |
| Edmonton M.B. | 0 | **45** |
| Norfolk | 48 | **81** |
| Norwich C.B. | 12 | **21** |
| Forehoe and Henstead R.D. | 11 | **22** |
| Walsingham R.D. | 0 | **22** |
| Surrey | 33 | **46** |
| Banstead U.D. | 0 | **28** |
| Wiltshire | 28 | **47** |
| Cricklade and Wootton Bassett R.D. | 17 | **35** |
| Yorkshire West Riding | 52 | **109** |
| Huddersfield C.B. | 15 | **36** |
| Sheffield C.B. | 11 | **22** |
| Glasgow | 152 | **144** |

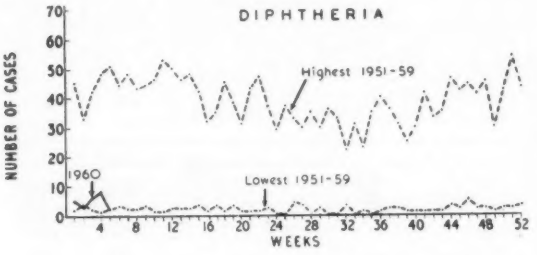
### Road Deaths in 1959

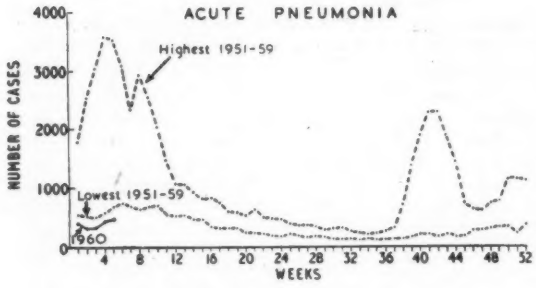
In December, 1959, 881 people were killed on the roads of Great Britain. This was 185 more than in the previous December. Of the total, 427 were pedestrians, 87 were cyclists, 143 were motor-cyclists, scooter or moped riders, or passengers, and 224 were drivers of motor vehicles or passengers.

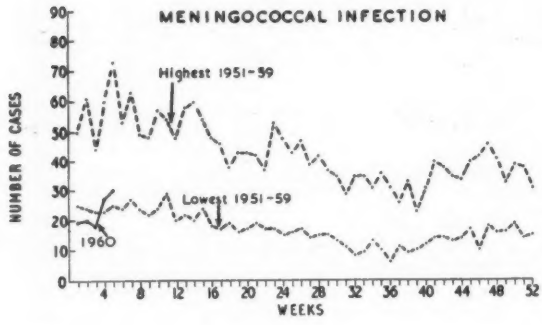
In 1959 as a whole 6,250 people were killed and 80,672 seriously injured, increases of 550 and 11,506 respectively on the previous year. Riders of motor-scooters and motor-cycles suffered the most serious increase in casualties. Altogether 1,592 riders and passengers lost their lives, compared with 1,582 drivers of motor vehicles or passengers.

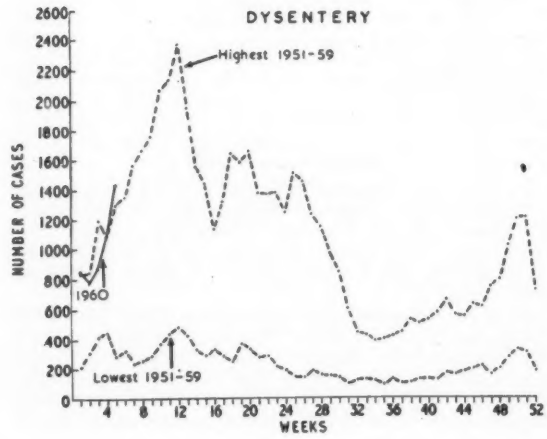
### Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus - - - - -, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.




## INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 30** (No. 4) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

| CASES | 1960 | | | | | 1959 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire |
| Diphtheria .. | 8 | 1 | 1 | 2 | 2 | 1 | 0 | 4 | 0 | 3 |
| Dysentery .. | 1,092 | 139 | 273 | 1 | 1 | 1,081 | 114 | 171 | 17 | 19 |
| Encephalitis, acute | 2 | 0 | | 0 | | 2 | 1 | | 0 | |
| Enteric fever: | | | | | | | | | | |
| Typhoid .. | 1 | 0 | 0 | 0 | | 1 | 0 | 1 | 0 | 1 |
| Paratyphoid .. | 4 | 0 | 1(B) | 0 | | 8 | 0 | 0 | 0 | 2(B) |
| Food-poisoning .. | 183 | 27 | 17 | 0 | | 157 | 12 | 5 | 0 | |
| Infective enteritis or diarrhoea under 2 years .. .. | | | | 7 | 13 | | | | 11 | 29 |
| Measles* .. .. | 1,200 | 29 | 19 | 7 | 1 | 18,025 | 1302 | 362 | 237 | 850 |
| Meningococcal infection .. .. | 27 | 3 | 7 | 0 | 2 | 31 | 1 | 12 | 0 | 3 |
| Ophthalmia neonatorum .. .. | 19 | 1 | 5 | 0 | | 19 | 5 | 5 | 0 | |
| Pneumonia† .. | 430 | 32 | 244 | 10 | 4 | 679 | 64 | 435 | 10 | 1 |
| Poliomyelitis, acute: | | | | | | | | | | |
| Paralytic .. | 5 | 2 | 0 | 0 | 0 | 20 | 2 | 1 | 0 | 1 |
| Non-paralytic .. | 1 | 0 | 0 | | | 1 | 0 | 0 | | |
| Puerperal fever§ .. | 234 | 33 | 18 | 0 | | 199 | 34 | 13 | 1 | |
| Scarlet fever .. | 1,265 | 56 | 115 | 38 | 37 | 1,396 | 87 | 82 | 33 | 41 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory .. | 393 | 55 | 68 | 10 | | 528 | 64 | 85 | 9 | |
| Non-respiratory | 60 | 2 | 9 | 3 | | 56 | 4 | 10 | 6 | |
| Whooping-cough | 967 | 114 | 160 | 6 | 60 | 859 | 27 | 49 | 76 | 151 |

| DEATHS | 1960 | | | | | 1959 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire |
| Diphtheria .. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Dysentery .. | 0 | 0 | | 0 | | 0 | 0 | | 0 | |
| Encephalitis, acute | | 0 | | | 0 | | 0 | | | 0 |
| Enteric fever .. | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | |
| Infective enteritis or diarrhoea under 2 years .. .. | 9 | 2 | 0 | 0 | 1 | 5 | 0 | 1 | 0 | 1 |
| Influenza .. .. | 43 | 2 | 1 | 0 | 1 | 54 | 2 | 8 | 0 | 2 |
| Measles .. .. | | 0 | 0 | 0 | 0 | | 1 | 0 | 0 | 0 |
| Meningococcal infection .. .. | | 0 | 1 | | | | 1 | 1 | | |
| Pneumonia .. | 766 | 46 | 33 | 22 | 9 | 815 | 81 | 64 | 21 | 14 |
| Poliomyelitis, acute | 1 | 0 | 0 | 0 | 0 | 1 | 0 | | 0 | 0 |
| Scarlet fever .. | | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory .. | 77 | 10 | 12 | 4 | 2 | 127 | 11 | 8 | 1 | 3 |
| Non-respiratory | | 1 | 0 | 0 | 0 | | 2 | 1 | 0 | 0 |
| Whooping-cough | 0 | 0 | 0 | 0 | | 1 | 0 | 0 | 1 | 0 |
| Deaths 0–1 year .. | 320 | 33 | 27 | 10 | 14 | 394 | 35 | 29 | 8 | 17 |
| Deaths (excluding stillbirths) .. | 11,689 | 948 | 734 | 153 | 192 | 13,112 | 1101 | 861 | 152 | 245 |
| **LIVE BIRTHS** .. | 14,400 | 1270 | 1001 | 248 | 440 | 14,515 | 1208 | 1069 | 241 | 408 |
| **STILLBIRTHS** .. | 270 | 16 | 24 | | | 324 | 25 | 22 | | |

* Measles not notifiable in Scotland, whence returns, are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

# Medical News

### Trial of Live Polio Vaccine

The Medical Research Council are shortly to carry out small-scale trials of the Sabin oral poliomyelitis vaccine in selected areas of Britain. This was announced in Parliament on February 15 by the MINISTER OF HEALTH.

### B.M.A. and World Refugee Year

At a recent meeting of the British Medical Association's International Relations Committee the question of whether there should be formal central support from the B.M.A. for World Refugee Year was discussed. It was decided that as many doctors were already active in local schemes it would be preferable to encourage local activities on behalf of refugees through the Divisions.

Britain has now reached her minimum target for World Refugee Year of £2m. and a new target of £4m. has been set. So far the United Kingdom has collected 10d. a head of its population, while the figure for Norway is 4s., for New Zealand 1s. 2½d., and for Sweden 1s. 1d.

### American Medical Students

Both the quality and the quantity of medical students in America have dropped in the last 10 years, according to Dr. R. A. MOORE, president of the Downstate Medical Centre of the State University of New York, who, in an interview with a special correspondent of *The Scotsman* (February 10), elaborated on statements he had made in a lecture at New York's Mount Sinai Hospital.

Since 1950, he said, the number of medical school applicants had dropped by one-third. In 1950–1 40% of new medical students had a college average of "A"; by 1957–8, the last year for which figures were issued, only 18% reached this level. He attributed the decline in applications to the pull of highly publicized professions such as science and engineering; the cost of medical education; and the out-of-dateness of much of the syllabus. Dr. A. C. MCGUINNESS, executive secretary of the New York Academy of Medicine, agreed that "some of our best brains are being attracted away from medicine to the physical sciences. Being a doctor does not carry the degree of prestige that it did and a boy choosing a career picks chemistry or physics, where he can always get a teaching job while studying for his Ph.D. and thus makes money instead of living like an undergraduate for eight years." He pointed out that, while there was an overall drop in the numbers of would-be medical students, major private medical schools, such as Harvard, still attracted more applicants than they could accept.

### Oberammergau and Berlin

The Secretary of the B.M.A. has unexpectedly received an offer of seats for Oberammergau on September 22, 1960, a date which would allow a group of doctors and their wives to visit the General Assembly of the World Medical Association in Berlin from September 15 to 20 and travel on to Oberammergau for the Passion Play on September 22. The approximate cost of the tour from London would be less than £100 per head, to include travel and hotel accommodation and the cost of admission to Oberammergau. The tour should be of interest to members of the profession, as it would include attendance as observers at the General Assembly of the W.M.A., sightseeing in Berlin and Munich, and a visit to the Passion Play. Further details may be obtained from the Secretary of the British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

### Hunterian Society

Sir CYRIL HINSHELWOOD, President of the Royal Society, proposed the toast to the Hunterian Society at the annual dinner held on February 11. John Hunter, he said, had the power of seeing special problems in the largest possible contexts. His great principle was that of experiment, "which did not fail in his age and won't fail in ours." He was unorthodox and would not have conformed at any time, especially in the present age of levelling down. Sir Cyril hoped that the Hunterian Society would go on being unorthodox for as long as possible. There was a great need for like-minded people to form societies for mutual and moral support. In reply, Mr. A. W. BADENOCH, the president of the Hunterian Society, briefly reviewed the year's work. He thought the society still managed to be somewhat unconventional and unorthodox. Sir EDMUND STOCKDALE, Lord Mayor of London, replying to Dr. Kenneth Robson's toast, explained the debt of gratitude he owed to the surgeons of St. George's Hospital, and after Dr. C. C. CHESTERMAN had proposed the health of the guests Lord RADCLIFFE, in a felicitous reply, mentioned that John Hunter was one of the first expert witnesses to give evidence in a murder trial, "and it didn't go down very well." He was the first of a long line of expert medical witnesses who had found an inherent incompatibility between scientific exactitude and the lawyer's demand for an answer, "Yes" or "No."

### Recognition Sought for Dr. Carlos Finlay

A Scottish physician's son, Dr. CARLOS J. FINLAY, who was born in Cuba in 1833, and who in 1881 was the first to demonstrate the part played by the mosquito in the transmission of yellow fever, is being nominated for election to the Hall of Fame for Great Americans, New York University, at the thirteenth quinquennial election in April.

The Hall—a 630 ft. colonnade—already houses among its 83 busts one of Dr. Walter Reed, who headed a commission which in 1901 confirmed the results of Finlay's research, and of Dr. W. C. Gorgas, who, as chief sanitary officer of the American Army, took steps to exterminate the mosquito in Cuba and Panama. Finlay's supporters believe that, though he is not an American citizen, Finlay, too, should be given a place of honour in the Hall of a country to which his discovery meant so much.

### Chadwick Trust

Surgeon Captain F. P. ELLIS, of the Medical Department of the Admiralty, has been awarded £100 and a medal by the Chadwick Trust in recognition of his outstanding work during the last five years in promoting the health of Royal Navy personnel.

### Scottish Health Services Council Chairman

The Scottish Health Services Council has appointed Mr. JOHN DUNLOP, O.B.E., C.A., F.F.A., as chairman. He succeeds Professor G. L. MONTGOMERY.

## COMING EVENTS

**Pharmaceutical Society of Great Britain.**—Scientific meeting: "Pharmaceutical Fellows of the Royal Society," by T. D. WHITTET, Ph.D. (chief pharmacist, University College Hospital, and lecturer in pharmacy, University College Hospital Medical School), at the Society's House, 17, Bloomsbury Square, London, W.C.1, 7.30 p.m., February 24.

**Medical Society for Study of Venereal Diseases.**—General meeting, February 26; 6.45 p.m., coffee; 7.30 p.m., Dr. G. L. MCELLIGOTT: "Venereal Disease and the Public Health." 11, Chandos Street, London, W.1.

**Association of School Medical and Dental Officers of Scotland.**—Annual general meeting, Glasgow, March 5: 10.30 a.m., the Art Galleries, Kelvingrove, an exhibition of children's art and talk with slide demonstration by Miss JEAN IRWIN on "Children's Art as a Guide to Personality"; 2.30 p.m., business meeting in the Grand Hotel after lunch there.

**"The Profession in Contemporary Society."**—Paper to be read by Mr. W. A. ALLEN, A.R.I.B.A. (superintendent

architect of Building Research Station), March 8, 6 p.m., Royal Institute of British Architects, 66, Portland Place, London, W.1. Members of the medical profession are invited to be present.

**Ileostomy Association, Scottish Division.**—Annual general meeting, March 12, 2.30–5 p.m., at the Scottish Tourist Board Hall, Rutland Place, Edinburgh. Details from the Secretary, 7, Randolph Cliff, Edinburgh.

**British Council for Rehabilitation.**—Course and conference in conjunction with the University of St. Andrews, at Queen's College, Dundee, March 29 to 31: "Rehabilitation—Its Industrial and Social Implications." Details from the general secretary of the Council, Tavistock House (South), Tavistock Square, London, W.C.1. (Euston 4037/8.)

**Faculty of Radiologists.**—Courses for candidates for the D.M.R.D. and D.M.R.T. (R.C.P. Lond., R.C.S. Eng.) starting in October, 1960, are now being organized by the Faculty of Radiologists. For details see *Journal*, advertisement p. 68.

## SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

### Sunday, February 21

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, postgraduate course for general practitioners. 2 p.m., Some Neurological Cases; 2.45 p.m., Dr. C. J. Earl: Nutritional Disorders of the Nervous System; 3.45 p.m., Mr. W. S. Foulds: Some Ocular Signs of Neurological Significance; 4.30 p.m., Dr. M. F. T. Yealland: Some Aspects of Epilepsy with Reference to the Electroencephalograph.

### Monday, February 22

GUY'S HOSPITAL: PHYSIOLOGY THEATRE.—5.30 p.m., endocrine demonstration: Diabetes Mellitus.

HUNTERIAN SOCIETY.—At Mansion House, 8.30 p.m., Hunterian Oration by Mr. C. Robert Rudolf: New Light on William Clift and His Contemporaries.

MANCHESTER MEDICAL SOCIETY.—(1) SECTION OF ODONTOLOGY: At Lecture Room, Dental Hospital, 4.30 for 5 p.m., Mr. H. Allred: An Aspect of the Morphology of Human Dentine. (2) SECTION OF GENERAL PRACTICE: At Large Anatomy Theatre, Manchester University Medical School, 8.30 for 9 p.m., Dr. M. C. G. Israëls: Pitfalls in the Diagnosis and Management of Blood Diseases.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Attempted Suicide.

### Tuesday, February 23

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. W. R. S. Doll: Epidemiological Methods in Leukaemia Research.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. L. Szur: Radiotherapy in Dermatology.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. Kenneth McLay: Tests of Acoustic Function I.

KEIGHLEY AND DISTRICT MEDICAL SOCIETY.—At General Hospital, Skipton, 8.30 p.m., Dr. S. T. Anning: Treatment of Leg Ulcers.

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Children's Department, Farnborough Hospital, 8 p.m., Dr. J. M. Tanner: Genetics, Environment, and the Growth of Children.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. J. A. Sharp: The Rhinencephalon.

LONDON UNIVERSITY.—At Queen Mary College, 1.30 p.m., Dr. Donald Hunter: Historical Perspective in Science and Medicine.

MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Manchester University Medical School, 4 for 4.30 p.m., University Lecture on the History of Medicine by Dr. J. N. Mills: "J. S. Haldane."

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Croonian Lecture by Dr. D. E. Denny-Brown: Diseases of the Basal Ganglia and their Relation to Disorders of Movement.

ROYAL SOCIETY OF HEALTH.—At Caxton Hall, Westminster, S.W., 2.30 p.m., discussion to be introduced by Dr. Brendan Moore: Sewage Contamination of Bathing Beaches.

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Manson Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. Crooks: Statistical Approach to the Diagnosis and Assessment of Therapeutic Response in Thyroid Disease.

UNIVERSITY COLLEGE LONDON.—At Chemistry Theatre, Gower Street, W.C., 5.30 p.m., Inaugural Lecture by Professor J. A. B. Gray: Place of Physiology in University Education.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. Colin Edwards: Neurology.

### Wednesday, February 24

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Laboratory Diagnosis of Mycotic Lesions.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Paul Wood: Chronic Constricted Pericarditis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. Kenneth McLay: Tests of Acoustic Function II.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. W. Badenoch: Surgery of Simple Enlargement of the Prostate.

LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., medical papers presented by Registrars.

●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, 8 p.m., Dr. W. H. Taylor: Renal Disease—Relation of Symptoms to Biochemical Findings.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Manchester University Medical School, 4 for 4.30 p.m., Presidential Address by Dr. R. W. Luxton: The Common Health.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. A. E. Mourant: Significance of Human Blood-group Distribution.

SOCIETY OF CHEMICAL INDUSTRY.—At 14, Belgrave Square, S.W., 6.15 p.m., joint meeting of Food and Microbiology Groups. Subject: New Methods of Factory Hygiene in the Food Industry. Papers by Mr. W. J. Blois-Johnson, B.Sc., and Mr G. A. Thomas, M.Sc.

### Thursday, February 25

BELMONT HOSPITAL CLINICAL SOCIETY.—8 p.m., Dr. Thomas Freeman: On the Psychopathology of Schizophrenia.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor Sheila Sherlock: Liver Failure.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., F. Ray Bettley: Lupus Erythematosus.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. Kenneth McLay: Tests of Vestibular Function I.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Mr. D. W. Bracey: Strip Gastrectomy: A Preliminary Report; Mr. F. C. Dwyer: Hallux Valgus and Rigidus in the Adolescent.

LONDON UNIVERSITY.—At Royal Free Hospital School of Medicine, 5.30 p.m., special university lecture in human anatomy and morphology by Dr. Sybil Cooper: Relations Between the Histology and the Physiology of Muscle Stretch Receptors.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Staff House, Manchester University, 7.45 for 8 p.m., Dr. T. Dinsdale, Mr. G. Ashcroft, and Dr. W. Ken Jones: Symposium on Dental Anaesthesia.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Croonian Lecture by Dr. D. E. Denny-Brown: Diseases of the Basal Ganglia and Their Relation to Disorders of Movement.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. H. Paterson: postgraduate demonstration in neurology.

WESTMINSTER HOSPITAL MEDICAL SCHOOL.—5.30 p.m., clinico-pathological conference. Symposium on Chronic Bronchitis.

### Friday, February 26

HEBERDEN SOCIETY.—At Nurses' Recreation Hall, 4 p.m., papers by Dr. Peter S. Davis, Dr. B. G. Parsons-Smith, Mr. J. C. F. Hindenach, Dr. Dr. H. Baron, Dr. George Brown for Dr. F. Dudley Hart, and Dr. O. Savage.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. B. Russell: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Sir Clement Price Thomas: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. Kenneth McLay: Tests of Vestibular Function II.

INSTITUTE OF NEUROLOGY.—4.30 p.m., Dr. John Foley: Hypertonus and Hyperreflexia.

KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Professor Sheila Sherlock: Diagnosis and Treatment of Portal Hypertension. (2) 4 p.m., Dr. J. A. Fraser Roberts: Medical Genetics II.

ROYAL INSTITUTION.—9 p.m., Professor Alexander Kennedy: The Scientific Lessons of Brainwashing.

### Saturday, February 27

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Addenbrooke's Hospital, Cambridge, postgraduate course for general practitioners. Symposium on Orthopaedics and Physical Medicine. At Lecture Room "B." *Morning:* 10.30 a.m., Mr. T. J. Fairbank: Children's Feet; 11.30 a.m., Mr. L. W. Godfrey: Synovitis of the Knee; 12.15 p.m., Mr. R. W. Butler: Treatment by Manipulation. *Afternoon:* 2.30 p.m., Mr. T. J. Fairbank: Brachalgia; 3 p.m., "Any Questions?"; 4 p.m., Dr. W. A. Fell: Home Management of Rheumatoid Arthritis.

### Sunday, February 28

COLLEGE OF GENERAL PRACTITIONERS.—At Littlewood Hall, General Infirmary at Leeds, 11 a.m., Mr. J. Foster: The Glaucoma Problem.

## BIRTHS, MARRIAGES, AND DEATHS

### BIRTHS

**Stone.**—On January 28, 1960, at Wanganui, New Zealand, to Barbara Mary (formerly Dana), M.B., B.S., and Arthur Richard Stone, M.R.C.P., M.R.A.C.P.—a son.

### DEATHS

**Bryan-Brown.**—On January 23, 1960, at 12, Cotswold Way, Enfield, Reverend Douglas Stephen Bryan-Brown, M.B., B.Ch., formerly medical missionary in China, aged 72.

**Easby.**—On January 28, 1960, Mary Lena Easby, M.B., B.Ch., of 172, Wells Road, Bristol.

**Gupta.**—On June 3, 1959, result of a railway accident, Asok Das Gupta, M.B., B.S.(Patna), of Chowra, Rasta, Jaipur, India.

**Hoey.**—On January 25, 1960, at 286, Wigan Lane, Wigan, William Hoey, M.B., B.Ch., aged 64.

**Lenson.**—On January 26, 1960, at Eastern General Hospital, Edinburgh, John George Lenson, M.B., Ch.B.Ed. (1959), of 11, Chollerford Avenue, Whitley Bay, Northumberland.

**MacCallum.**—On November 22, 1959, in Sydney, Australia, Walter Paton MacCallum, C.B.E., D.S.O., *M.C.*, E.D., F.R.A.C.P.

**Mac Feat.**—On February 10, 1960, at Bogueside, Douglas, Lanarkshire, George Mac Feat, O.B.E., M.B., C.M., aged 86.

**Meyerhof.**—On January 27, 1960, at 20, Watchfield Court, London, W., Karl Meyerhof, L.R.C.P.&S.Ed., L.R.F.P.S., aged 68.

**Murphy-O'Connor.**—On January 17, 1960, at Ardmore, 17, Parkside Road, Reading, Berkshire, Patrick George Murphy-O'Connor, M.B., B.Ch., aged 68.

**Pearce.**—On January 20, 1960, at Central Middlesex Hospital, Reginald Hickmott Pearce, M.R.C.S., L.R.C.P., of White Walls, Woodland Walk, Ferndown, Dorset.

**Pratt.**—On January 18, 1960, at Baldersby St. James, Thirsk, Yorks, Thomas Dawson Pratt, M.R.C.S., L.R.C.P., formerly of Ripley Lodge, Wortley, Leeds.

**Proctor.**—On January 23, 1960, Winifred Mary Proctor, M.B., B.S., of 40, Herne Hill, London, S.E.

**Richards.**—On January 19, 1960, in a Malvern nursing-home, John Evans Richards, M.B., of 1, Cawl Barn Cottages, Colwall, Worcs, aged 84.

**Watt.**—On January 5, 1960, at "Strathyre," Nairn, Patrick Mitchell Watt, M.B., Ch.B.

**Wilson.**—On January 17, 1960, William Frank Wilson, M.B., B.S., of 44, The Drive, Hove, Sussex, aged 79.

# Any Questions ?

*We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.*

## Diagnosing Metabolic Errors by Urine Analysis

**Q.**—*What "inborn errors of metabolism" may be suspected or diagnosed by routine or special examination of the urine?*

**A.**—Assuming "inborn errors of metabolism" to indicate an abnormality caused by a deficiency or altered structure of a specific enzyme or group of enzymes due to genetic factors, and restricting them to those whose effects can be seen in the urine, it is convenient to group them into three classes.

CLASS I

| Condition | Abnormal Substance | Tests |
|---|---|---|
| Alkaptonuria .. | Homogentisic acid | Reduces Fehling's solution. Urine darkens on standing. Napkins stain red |
| Tyrosinosis .. | Hydroxyphenylpyruvic acid | Positive Millon test. Paper chromatography |
| Hartnup disease .. | Abnormal indole compounds. Excess amino-acids | Paper chromatography |
| Maple syrup disease | Abnormal hydroxy acids. Excess leucine and valine | Unusual smell of urine. Paper chromatography |
| Phenylketonuria (phenylpyruvic oligophrenia) | Phenylpyruvic acid and other abnormal derivatives and phenylalanine metabolism. Abnormal indole derivative | Green colour with ferric chloride ("phenistix"). Paper chromatography |
| Porphyria congenita | Uroporphyrin I | Red urine—special tests |
| Porphyria acuta .. | 1. Porphobilinogen | 1. Red colour with Ehrlich's aldehyde reagent; special tests |
| | 2. In acute attack uroporphyrin III | 2. Red colour—special tests |

CLASS II

| Condition | Abnormal Substance | Tests |
|---|---|---|
| Wilson's disease .. | Amino-acid in excess. Copper excretion increased | Paper chromatography. Special tests |
| Adrenal hyperplasia (in infants) | Abnormal steroids and pregnanetriol in excess. 17-ketosteroids increase. There are several types of error, giving rise to differential steroid patterns | Special tests |
| Galactosaemia .. | Galactose | Reduction of Benedict's but no reduction using specific ferment as in "clinistix." Confirming tests |
| Cystinosis (cystine storage disease) (Lignac-Fanconi disease) | Excess amino-acid, glucose and bicarbonate etc. | Alkaline urine. Low Sp. G. Reduction of Benedict. Chromatography. |
| Diabetes mellitus "juvenile type" | Glucose. Ketone bodies | Benedict's reduced +++. Sp. G.—high. Ketone bodies |
| Sucrosuria .. .. | Sucrose | Reduction of Benedict's after hydrolysis with HCl |
| Fructosuria .. | Fructose | Reduction of Benedict's but not "clinistix" |
| Pentosuria .. .. | Various pentoses | Weak reduction of Benedict's. Beal's test, etc. Chromatography |

CLASS III

| Condition | Abnormal Substance | Tests |
|---|---|---|
| Cystinuria .. .. | Cystine, lysine, valine and arginine in excess | Cystine crystals in deposit. Stone formation. Special tests |
| Renal glycosuria .. | Glucose | Benedict's reduced. Ketones rare |
| Fanconi syndrome | Excess amino-acid, glucose, bicarbonate | Dilute alkaline urine. Benedict's reduced. Amino-acids in chromatography |
| Renal acidosis .. | Excess bicarbonate | Dilute alkaline urine |
| Nephrogenic diabetes insipidus | Inability to concentrate urine | Dilute low Sp. G. urine even after water deprivation |

## Dermatitis from Clothing

**Q.**—*Apparently some underclothing and socks cause irritation of the skin and even dermatitis when worn without being first washed. Do some manufacturers add any substance which might cause this trouble?*

**A.**—Dermatitis from clothing is a very real entity and results from a variety of causes. In some cases it is produced by chromium salts which have been used in the process of dyeing the material. Sometimes it is the dye itself, and dermatitis from nylon stockings is produced in this way. Some fabrics in contact with the skin actually leave visible dye on the skin, particularly in the presence of moisture, and this also may cause dermatitis. Some types of material are impregnated with resins either to improve their appearance or to impart a non-creasing quality. Non-creasable neckties can cause allergic sensitivity of the skin and the same has been reported of underpants treated in this way. The precise nature of substances added to cloth to improve its various qualities is, of course, a trade secret which manufacturers might not be anxious to reveal.

The irritation caused by substances of this kind will probably always depend upon the development of allergic sensitivity on the part of the wearer, and the number of people affected will therefore be a small proportion of those exposed. In order to establish allergic sensitivity in the first place one would expect the textile to be rather heavily impregnated with the offending material. A first washing with water would be likely to remove a considerable amount of this and to make the development of sensitivity less likely. Once the skin has become sensitive it may be extremely so, and often even repeated washing might then not be sufficient to allow the garment to be tolerated.

## Smoking and Migraine

**Q.**—*A woman who is prone to migraine attacks finds that when she smokes only one cigarette very occasionally it is always followed the next day by fatigue, headache, and sometimes even a migraine attack, with prodromal scotomata. Why is this?*

**A.**—This question contains an interesting observation, but it is impossible to answer it. What effects of smoking do we know which might provide a clue? In the first place, smoking causes a liberation of the antidiuretic hormone from the posterior lobe of the pituitary body. This hormone causes some vasoconstriction but it is quickly destroyed, and it seems unlikely that the liberation of this hormone could cause symptoms the following day. In the second place, smoking causes a liberation of noradrenaline from chromaffin tissue. It is conceivable that, if such a liberation takes place in the brain in a subject in whom the store of noradrenaline in chromaffin tissue is small, the symptoms of fatigue, etc., which are described might follow. The fact that migraine can be treated by caffeine and ergotamine seems consistent with such a view. Perhaps migraine is due to a lack of noradrenaline in chromaffin stores in the brain.

## Double Vaccination

**Q.**—*Why is it usual to avoid double vaccination? I have in mind vaccination with B.C.G. when poliomyelitis vaccine is being given.*

**A.**—There is much uncertainty and some confusion in this matter. On the one hand, three antigens are frequently given simultaneously to infants (in the form of diphtheria–tetanus–pertussis vaccine), and trials of a quadruple vaccine (including the poliomyelitis component) are now in progress in this country. In France and Canada this quadruple vaccine has been used for some time and is said to be very effective and free from reactions.

On the other hand, there are those who believe that antigens are at their best when given singly, when there can be no interference phenomena. As a general principle it

could be argued that this is the most desirable policy, but it is seldom practicable—it involves far too large a number of single injections (and visits to the clinic).

In the particular case, however, of B.C.G. vaccination during a course of poliomyelitis injections it is probably advisable to space the B.C.G. at least a month away from any of the poliomyelitis inoculations. This is because B.C.G. vaccine is not so simple a prophylactic as, say, diphtheria toxoid: it is a living culture of bacilli, and it produces quite a distinct reaction. It is also a vaccine of which experience is still comparatively limited. In the same way as it is desirable to separate smallpox vaccination from other inoculations, B.C.G. vaccination should be timed, as it is usually convenient to do, in such a way as not to affect, or be affected by, any other antigenic stimuli.

### Codeine Phosphate for Bowel Irritability

**Q.**—*In a case of persistent loose stools due to early diverticulitis, is the prolonged use of tab. codein. phos. ¼ gr. daily in any way harmful?*

**A.**—There is no doubt that codeine phosphate is the best single drug for bowel irritability, and, given in small doses over quite long periods, it does not appear to be harmful. Bulk-regulators, such as methylcellulose ("celevac") or "i-so-gel," may sometimes reduce the need for it.

### Disinfection with Ultra-violet Light

**Q.**—*Would exposure of woollen, silk, and nylon objects made by sanatorium patients to an ultra-violet lamp for one hour at a distance of three feet (0.9 m.) satisfactorily kill tubercle bacilli?*

**A.**—It is well known that exposure to ultra-violet light will kill *Mycobacterium tuberculosis*. It is, however, mainly used for sterilizing the atmosphere and dealing with bacilli carried in dust and droplets. It might well be ineffective for sterilizing objects made by patients because it would be impossible to ensure that every part of each object was exposed to the light. Similarly, bacilli in folds or interstices of material might remain untouched. The same considerations apply to disinfecting a room. Exposure to formalin vapour is a much safer method of disinfecting a room, and is also simple and cheap.

### Suppressing Lactation with Hexoestrol

**Q.**—*What is the recommended dosage of intramuscular hexoestrol for suppression of lactation?*

**A.**—The dose of hexoestrol dipropionate for this purpose is 15 mg. intramuscularly; it might have to be repeated once or twice. Many doctors prefer to follow the injection by oral stilboestrol or ethinyloestradiol for five or six days, while others find these oral preparations sufficient without a priming injection. Stilboestrol is given 5 mg. four times daily for two days, then three times daily for two days, then twice daily for two days. Ethinyloestradiol is given similarly, each dose being 0.1 mg.

### Inheritance of Angioneurotic Oedema

**Q.**—*What chances of being affected would there be for the children of a man who suffers from periodic attacks of angioneurotic oedema? His grandparents were unaffected; his father died of oedema of the glottis; his mother was unaffected. He has a brother unaffected and a sister mildly affected.*

**A.**—Angioneurotic oedema usually behaves, as in this family, as if due to a dominant mutant gene. The risks to this man's children are, therefore, 1 in 2. Numerous dominant pedigrees are on record, one of the earliest being that reported by Osler.[1]

REFERENCE

1 Osler, W., *Amer. J. med. Sci.*, 1888, **95** n.s., 362.

## NOTES AND COMMENTS

**Ultrasonics in Physiotherapy.**—Dr. A. W. BAUER (London, W.1) writes: Enthusiasm for this treatment has not largely died down ("Any Questions?" November 7, 1959, p. 967) Work on the subject is going on in the U.S.A. and on the Continent, and I myself have written about it.[1–6] It is a little surprising that the writer of the answer on this subject omitted the main indications for ultrasonic therapy—that is, disorders of the circulation such as frostbite and Raynaud's disease, myalgias and neuralgias due to osteochrondrosis, spondylosis and arthrosis of the spine. It is probable that ultrasonic energy applied to these latter diseases of the locomotor and skeletal system improves the nutrition of cartilaginous tissue and of disks. In any event, the good results achieved in these conditions by myself (and others) during the past nine years are very superior to those obtained by diathermy, short-wave, and other heat therapies. It is impossible to equate the thermal effect of ultrasonic energy with heat therapy in such a casual manner. The rise of temperature in the tissue can be minute in therapeutic doses of ultrasonic energy.[4] Moreover, ultrasonic energy possesses a selective effect on living tissue and a specific action on blood supply via the autonomous nervous system. In therapeutic doses, ultrasonics are not dangerous.

AN EXPERT writes: I think there are few workers in America and England who support the theory that ultrasonics has any special properties, either in its direct action or via the autonomic nervous system, which cannot be explained on the basis of selective tissue heating. This heating is selective by virtue of the physical properties of the ultrasonic beam and its effect is therefore somewhat different from that of short-wave diathermy. Disorders of the circulation would not feature high on my own list of indications for ultrasonic treatment. Improvement in spinal conditions has certainly not been proved to be due to improved nutrition of disks and cartilage, although this theory has been put forward in some quarters. In this country few of these conditions are treated by any form of thermotherapy alone, but rather in combination with traction, exercises, support, etc. Most authorities on ultrasonics agree that heating of the spine (or any bony structure) is more efficient in the case of ultrasonics than other forms of thermotherapy. If heating methods *per se* are compared as the sole method of treatment, as Dr. Bauer has done, I should expect the results to be superior in the case of ultrasonics. Although the first enthusiasm has worn off, there are over 500 generators in regular use in this country, although few specialists in physical medicine use them. Ultrasonic treatment is as safe as short-wave diathermy in the hands of qualified operators.

REFERENCES

1 Bauer, A. W., *Brit. J. phys. Med.*, 1951, **14**, 145.
2 —— ibid., 1952, **15**, 1.
3 —— ibid., 1953, **16**, 199.
4 —— ibid., 1954, **17**, 97.
5 —— ibid., 1957, **20**, 151.
6 —— in *British Encyclopaedia of Medical Practice*, 1952, interim supplement 117.

**Correction.**—The date of Dr. R. M. Stewart's paper in *J. Neurol. Psychopath.*, mentioned in the answer to a question on the Morgagni-Stewart-Morel syndrome ("Any Questions?" February 6, p. 441), was wrongly printed as 1938. It should have read 1928.

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